CORONARY HEART DISEASE IN YOUNG ADULTS

A MULTIDISCIPLINARY STUDY

CORONARY HEART DISEASE IN YOUNG ADULTS

A MULTIDISCIPLINARY STUDY

By

Menard M Gertler, M D

and Paul D White, M D

WITH THE AID ADVICE, AND
EDITORIAL ASSISTANCE OF
E F BLAND M D
J FERTIG PH D
S M GARN PH D
J LERMAN M D
S A LEVINE M D
H B SPRAGUE M D
N C TURNER M SC



Published for The Commonwealth Fund
By Harvard University Press
Cambridge, Massachusetts, 1954

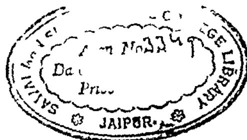
THIS STUDY WAS CONDUCTED AT

Massachusetts General Hospital
and Harvard Medical School

Published for
The Commonwealth Fund
By Harvard University Press
Cambridge Massachusetts

For approximately a quarter of a century THE COMMONWEALTH FUND through its Division of Publications sponsored edited produced and distributed books and pamphlets germane to its purposes and operations as a philanthropic foundation On July 1 1951 the Fund entered into an arrangement by which HARVARD UNIVERSITY PRESS became the publisher of Commonwealth Fund books assuming responsibility for their production and distribution The Fund continues to sponsor and edit its books and cooperates with the Press in all phases of manufacture and distribution

Distributed in Great Britain
By Geoffrey Cumberlege
Oxford University Press
London



LIBRARY OF CONGRESS CATALOG CARD NO 54 8625

MANUFACTURED IN THE UNITED STATES OF AMERICA

DEDICATED

to the prolongation of the life
and to the protection of the health
of the young coronary candidate himself

Preface

THIS monograph presents a summary of an interdisciplinary research on coronary heart disease begun in 1946 under the auspices of seven physicians Four on the medical staff of the Massachusetts General Hospital Boston represented in particular the cardiovascular and metabolic fields Drs Edward F Bland, Jacob Lerman Howard B Sprague and Paul D White The three others were Dr Samuel A Levine of the Peter Bent Brigham Hospital Dr Stanley M Garn of the Department of Anthropology of Harvard University referred to the project by Professor Ernest A Hooton, chairman of that department and Dr Fred Alexander Assistant in Medicine at the Massachusetts General Hospital who carried out pilot examinations of the first twelve patients studied During the first year the financial support came from the Cardiac Research Fund of the Massachusetts General Hospital As plans developed and the research grew in scope it was necessary to assign a full time medical worker to the project and to seek aid to defray the mounting expenses Happily Dr Menard M Gertler was available as full time director of the study Dr Garn was also able to devote much time and energy to it during more than two years The Commonwealth Fund made a generous allocation to support the research from January 1 1948 through May 1950 and to publish the present monograph. Valuable help has come through consultation, from Dr James B Hamilton Professor of Anatomy the State of New York Medical College Brooklyn N Y and from Dr Alan M Butler and Miss Margaret Rourke of the Laboratory Department of the Massachusetts General Hospital We are also greatly indebted to Dr John Poutas and to the executives of the Lever Brothers Company in Cambridge Mass for making available individual subjects for our unmatched and matched control study To the executive staff of Filene s Department Store Boston and to the medical staff the authors are indebted for the cooperation given during the selection of additional individuals who were necessary to complete the matched control group To Dr John Fertig we are all very grateful for his generous advice and painstaking efforts in the final preparation

of the manuscript We are happy, also to acknowledge the advice co-operation and assistance of the Division of Publications of the Commonwealth Fund

It is a pleasure to express grateful appreciation to all those mentioned above and to the secretaries and technicians (Miss Sally Poor Mrs Allison Walker Mrs Jennifer Lehmann Mrs Neria Ryder Mrs Mary Clapp Miss Adeline Flavio Mrs Estelle Neidle and Miss Helen Donovan) who labored long and faithfully in the completion of the study We are grateful to Mrs Naomi C Turner for her investigations on the salivary oxidation reduction potential in relation to coronary heart disease It is also a pleasure to acknowledge the assistance of Dr Richard Howard Commander Morgan Driskell and Dr Jay Lockwood who helped in various aspects of the study It is hoped that after some years of follow up a brief report can be made on the control group of subjects with particular reference to their state of health at that time

PAUL D WHITE

Boston Mass
March 1954

Contents

Figures

Tables

CHAPTER III FAMILY INCIDENCE THE ROLE OF HEREDITY AND RACE

CHAPTER IV ANTHROPOMETRIC AND MORPHOLOGICAL APPRAISAL OF PHYSIQUE

CHAPTER V ATHLETIC ACTIVITY AND OCCUPATIONS

CHAPTER VI FINDINGS ON MASCULINITY

CORONARY HEART DISEASE IN YOUNG ADULTS

A MULTIDISCIPLINARY STUDY

CHAPTER I

Introduction The Problem and the Procedure

HEART disease due to coronary atherosclerosis is a major problem in the world today Cardiovascular renal diseases now claim as their victims half of all those who die in the United States The percentage reported by the Public Health Service for the United States Registration Area was 49 5 in 1948 and 52 0 in 1950—much greater than the sum of the deaths from the next four causes cancer accidents tuberculosis and pneumonia Although owing in large part to the steadily increasing control of infectious diseases a greater number of persons now reach old age when cardio vascular diseases are prone to occur there are still many thousands who die of heart disease in youth and middle age

One of the most perhaps *the* most important and common kinds of heart disease results from atherosclerosis of the coronary arteries It is most surprising that relatively little intensive research has been carried out in the past concerning the etiology of this vitally important hazard to the life of man Only a rare person like Dr Timothy Leary of Boston had taken an active interest in the subject before the past few years when other worthwhile studies of the fundamental causes of the disease commenced to engage the interest and talents of serious workers The present research we venture to believe is such a study but even it like several others in the field, has but scratched the surface uncovering problems that need still deeper thought and study

The background of the present study extends to 1937 when Glendy Levine and White published a report briefly analyzing 100 patients under the age of 40 who had coronary heart disease and comparing them with a group of healthy old persons In the search for clues two important findings stood out (*a*) there were 96 males and only 4 females in the coronary group out of a population having equal numbers of males and females and (*b*)

the majority of the patients were of husky that is mesomorphic build Another interesting fact was that the healthy old people had had in youth many more infectious diseases such as diphtheria and typhoid fever, than had the coronary patients Further study of these groups was prevented by preoccupation with World War II, but the problems continued to be turned over in the minds of the investigators as is evidenced by the question asked by White in the third edition of his textbook *Heart Disease* published in 1944 Why should the robust and apparently most masculine young male be particularly prone to this disease? Incidentally Levine in 1929 working with Brown had described the type of male especially subject to coronary thrombosis as short, thickset and obese with thick wrists

On the basis of these earlier interests and because of the compelling challenge of this increasingly serious disease a new research study of coronary atherosclerosis in youth was organized as soon as postwar conditions permitted Many clues which hung together loosely had been uncovered by previous studies on coronary heart disease This project was conceived (*a*) to study more intensively the existing clues and (*b*) to unite in a more cohesive fashion the various disciplines from which these clues stemmed Accordingly coronary heart disease was studied from the following viewpoints sex selection and the morphological genetic athletic, occupational physiological psychological clinical dietary, hormonal and biochemical aspects

It was obvious that the relation of sex to the problem needed to be studied further and it was for this reason that the advice and cooperation of Dr James B Hamilton were sought Biochemical and metabolic studies were carried out in the laboratories of the Massachusetts General Hospital by Miss Margaret Rourke Physical and psychological examinations complete histories including the factor of diet x ray films and electrocardiograms were secured with the cooperation of all concerned The question of heredity was also studied

Selection of Patients

An upper age limit was set in the belief that the individual who had a coronary occlusion at an early age would show predisposing characteristics The maximum age used by Glendy White and

TABLE 1–1 Sources of patient referrals to the coronary research project

	No of patients
Project advisors	27
M G H associated cardiologists	12
Out patient and house records	4
Self referral*	1
Referring cardiologists	36
Veterans Administration	20
TOTAL	100

Applied for the study following a newspaper description of the project.

Levine was retained 40 years or less at the time of myocardial infarction and less than 50 at the time of examination The limit was set at 40 rather than 35 or 30 as a matter of convenience in obtaining enough patients Although the youngest patient in the series was 22 at the time of his myocardial infarction the majority *(61 out of 97 males) had their myocardial infarction between the* ages of 35 and 40

Patients were accepted for study in the Coronary Research Project only if they fulfilled certain other requirements in addition to those of age ambulatory physical condition history of myo cardial infarction at least six months earlier and absence of dia betes of syphilis or other serious infections and of hypertension at the time of the study (one patient had undergone a successful *lumbodorsal sympathectomy for previous hypertension)* The 100 patients accepted in the study and discussed in these pages are those who met these requirements out of approximately 250 referrals

At the beginning of the project patients were referred by mem bers of the Advisory Board from their private and clinic practices and from the Out Patient Department of the Massachusetts Gen eral Hospital In all 31 patients (see Table 1) came from the practices of five cardiologists and the hospital files An addi *tional 12 patients* were referred by cardiologists associated with the Cardiac Laboratories of the Massachusetts General Hospital and 1 patient was self referred After 44 patients had been obtained it was necessary to seek elsewhere for sufficient material Accord ingly cardiologists who had attended graduate and other courses at the Cardiac Laboratories of the Massachusetts General Hospital were circularized With their aid, 36 patients were obtained (from

TABLE 1-2 Geographical distribution of 100 coronary heart disease patients

Home state	*No of patients*	*Home state*	*No of patients*
Massachusetts	61	Florida	1
New York	8	Alabama	1
New Jersey	5	Ohio	1
Connecticut	4	Illinois	1
Pennsylvania	4	Colorado	1
Maine	3	Kansas	1
Rhode Island	3	Mississippi	1
Texas	2	North Carolina	1
Kentucky	1	South Carolina	1

Texas to Maine) and also entered the hospital for the study All patients participated in the project without expense to themselves With the cooperation of Dr David Littman of the Veterans Administration an additional 20 patients were obtained from various parts of the country In this way no one social ethnic or economic group of patients constituted the entire series

The geographical distribution of patients indicated the same trend toward dispersion of source While 61 per cent of the patients came from the Commonwealth of Massachusetts (including the Veterans Hospital at West Roxbury and the Murphy Army General Hospital) and 10 per cent more came from three other New England states the remaining 29 per cent were from the rest of the United States (see Table 2)

Procedure for examination

Patients meeting the requirements were admitted to the Massachusetts General Hospital at the rate of two or three a week for a period of 24 to 72 hours During this time the tests evaluations and interviews were conducted without haste or pressure in order to allow the patient sufficient recovery time between tests Since almost all the patients had been hospitalized in the past the hospital routine was familiar to them The majority found the tests and interviews interesting and gave wholehearted cooperation not only during the period of this study but also in the follow up studies Two patients whose cooperation was unsatisfactory have shown excessive neurosis and in the case of one low grade psychosis

Upon arrival on the ward floor at 1 P M the patient was given a

series of thorough interviews medical questions stressing health history diet and habits a social interview stressing environment and upbringing an hereditary interview stressing family diseases and ages of death a psychological interview attempting to uncover sources of tension, and a detailed resume of events previous to and during the myocardial infarction The latter material in conjunction with the questionnaires forms the basis for several clinical papers in this series In addition to the direct interviews described a pencil and paper test (the Terman Miles see Chapter VI and Appendix A) and a questionnaire were given to the patient to be filled out during the stay The long interview we found not only served as a method of breaking the ice and obtaining important data but also seemed to improve the patient s emotional status

The patient went to his room at about 4 00 P M to begin the urine collection for the 17 ketosteroid determination In some cases radioactive iodine was administered at this time for the thyroid function test A basal metabolism test was made in the morning and if unsatisfactory for any reason was repeated on a subsequent morning Following breakfast a routine x ray film was taken and fluoroscopy carried out before lunch the electrocardiogram was taken (three standard limb leads three unipolar limb leads and six unipolar precordial leads) Blood smears for a differential count were also taken before lunch

Following the noon meal morphological anthropometric and somatotype studies were made Two hours after lunch the salivary redox test was taken five hours after lunch 25 cc of blood were drawn and held under refrigeration prior to biochemical analysis The patient was then discharged

In addition to the hospital study mentioned here subsequent recalls permitted re examination of about half the patients while repeated serum cholesterol determinations were made in the majority of cases with the cooperation of the patients and their physicians

Selection of Controls

A general group which will be referred to as the unmatched control group of 146 males of age occupation and ethnic origin similar to those of the coronary disease group was employed at the outset of this study However for many purposes it was deemed more satisfactory to adopt the experimentally ideal matched pair

technique as closely as possible since such variables as occupation race and physique might account for some of the differences between patients and unmatched controls * Therefore the matches to the coronary patients were made on an individual basis each matched control resembled some coronary patient in age, height weight body build ethnic origin, and occupation This group of 97 males will be known as the matched control group † The procedure for matching was as follows

1 *Age* The matched control for each patient was rarely more than 3 years older or younger At the most a 5 year difference was allowable if all other criteria were fully satisfied The two groups compared very closely in age the mean difference being 0 7 years

2 *Height* The match was held within 3 cm in the majority of cases the mean difference between the two groups was 2 57 cm

3 *Weight* Matching was done within 4 5 kilos (9 9 pounds) on the average the matched controls (who were taller) were 2 7 kilos (5 9 pounds) heavier, but the ponderal index or height/cube root of weight ratio was the same for the two groups

4 *Body build* This was considered to be very important, and careful matching was done In general the matched control was within a half point of the patient in each component (see Chapter IV for the method of evaluating physique) At no time was there a reversal of dominance as represented by the three components of physique (Sheldon et al 1940) (*a*) endomorphy (soft round obese build) (*b*) mesomorphy (hard, square muscular build), and (*c*) ectomorphy (fragile thin linear build)

5 *Race* Each match was of the same racial and national origin as was his index patient

6 *Occupation* Since exact matches could not be made for many unusual occupations (leatherette worker for instance), matching was done on the basis of a similar level of physical exertion Hence laborers were paired with laborers professional men with professional men and so on

*For example lipid levels vary not only with the presence or absence of coronary heart disease but also with differences in age and body build and possibly (though not definitely) with race It is therefore possible that variables other than the disease state could result in a difference between coronary disease patients and a general group of unmatched individuals

†Since a group of only 3 women was too small for significant comparison with a group of 97 men no attempt was made to provide matched controls for the women

With six variables to consider in each match the process was a tedious and sometimes difficult one as for example in the finding of a match for a 39 year-old mesomorphic Armenian waiter who came to Boston in 1930

It was not possible to employ the matched pair technique for all studies basal metabolic rate and athletic histories were analyzed for the patients only and a series of unmatched controls was used in evaluating urinary 17 ketosteroids The source of the control group in each instance will be stated in the text

REFERENCES

GLENDY R E LEVINE S A and WHITE P D Coronary disease in youth comparison of 100 patients under 40 with 300 persons past 80 *J A.M.A* 109 1775–1781 1937

LEVINE S A and BROWN C L Coronary thrombosis its various clinical features *Medicine* 8 245–418 1929

SHELDON W H STEVENS S S and TUCKER W B *The Varieties of Human Physique* Harper & Bros New York, 1940

WHITE P D *Heart Disease* 3rd Ed Macmillan Co New York 1944

CHAPTER II

Clinical Appraisal of the Coronary Group

IT is the purpose of this chapter to describe the 100 coronary heart disease patients studied with respect to certain variables such as sex age occupation and so on to analyze the character and mode of onset of both the premonitory symptoms and the acute prodromal symptoms and to describe the clinical findings at the initial examinations in 1949

Composition of the Group

Sex

Of the 100 patients examined 97 were men and 3 were women These proportions are almost the same as had been reported previously by Glendy Levine and White (1937) in a group of 100 persons who had experienced myocardial infarction prior to the age of 40 they found the ratio of men to women to be 96 to 4 Discussion of the relation of masculinity to coronary heart disease will be reserved for Chapter VI

Age

In the present study the 3 women examined were 35, 39, and 40 years of age The ages of the 97 men at the time of the acute episodes ranged from 22 to 40 years averaging 35 4 There were 8 men between 20 and 29 years 28 men between 30 and 34 years and 61 men between 35 and 40 years The age at the time of examination ranged from 24 to 51 years with an average of 38 2 The lapse of time between onset of myocardial infarction and our examination is given in Table 1

Race

The question of racial predisposition to coronary heart disease is far from being answered The selection of patients for study the

TABLE II–1 Lapse of time between onset of myocardial infarction and our initial examination of 97 male patients

Years	No of patients	Years	No of patients
0 5 – 1 0	17	5 51– 6 0	3
1 01– 1 5	14	6 01– 6 5	3
1 51– 2 0	15	6 51– 7 0	3
2 01– 2 5	8	7 01– 7 5	4
2 51– 3 0	8	7 51– 8 0	2
3 01– 3 5	2	8 01– 9 0	3
3 51– 4 0	4	9 01–10 0	2
4 01– 4 5	3	10 01–11 0	0
4 51– 5 0	4	11 01–12 0	1
5 01– 5 5	0	26 01–27 0	1

This man was examined by Dr H B Sprague in 1923

origin of the various reports and the interpretation of the final results all complicate the issue These questions and other problems concerning race in relation to coronary heart disease are more fully discussed in Chapter III

Nearly all the ethnic groups present on the east coast (the home of 70 per cent of the patients) were represented in this series (see Chapter III Table 6) The progenitors either male or female of nearly half the group originated in the British Isles Individuals of Mediterranean or Eastern Mediterranean origin comprised 37 per cent of the entire group a proportion well in excess of their representation in the areas from which the sample was drawn (Hooton 1950)

Occupation

Several reports in the literature have been concerned with unravelling evidence of a causal relationship between coronary heart disease and occupational pursuits (Yater et al 1948 Gordon et al 1939) This question is considered in greater detail in Chapter V Suffice it to say at this juncture that it is evident from this study that there are excessive numbers of patients in certain occupational categories the managerial comprises 42 per cent the semiprofessional 7 per cent professional (including doctors) 11 per cent semiskilled labor 30 per cent skilled 4 per cent and unskilled 3 per cent Thus in this limited series as in other more extensive series certain types of occupation are found to predominate

TABLE II-2 Distribution by month of acute episodes of myocardial infarction in 100 patients (97 male and 3 female)

Month	No of patients
January	13
February	4
March	11
April	5
May	13
June	1
July	7
August	4
September	10
October	9
November	12
December	11

Incidence and Symptoms

Incidence of infarction

The distribution of cases by month is shown in Table 2 The onset of acute episodes of coronary heart disease in our patients during the fall and winter months showed a greater absolute incidence which on statistical analysis is significant

The series of patients studied however, is too small to warrant the drawing of definite conclusions concerning the relation of weather to coronary episodes

As can be seen from Table 3 which gives the distribution of the acute episodes by time of day the majority occurred during the hours of increased activity with the greatest incidence in the early afternoon There appeared to be a decline in the rate of occurrence of myocardial infarction between the hours of 3 P M and 6 A M

TABLE II-3 Incidence of myocardial infarction by time of day in 100 patients (97 male and 3 female)

Time	No of patients	Time	No of patients
A M midnight-3	8	P M noon-3	27
3-6	5	3-6	10
6-9	17	6-9	11
9-noon	12	9-midnight	10

TABLE II–4 Symptoms preceding myocardial infarction in 64 male patients*

Symptom	*No of patients*
Angina pectoris	41
on effort	32
on emotional strain	5
after heavy meals	2
at rest	2
Pain radiating from chest	15
to arms	14
to shoulders	1
Dyspnea on exertion	22
Fatigue	7
Indigestion (upper abdominal distress)	20
after exercise	9
after eating	8
on emotional strain	3
Nervousness (tachycardia or palpitation)	4

36 patients (33 male and 3 female) had no symptoms prior to the acute episode

Symptoms

Of the 64 patients who gave a history of their symptoms preceding the acute episode (see Table 4) 8 said that the complaints had been present for longer than one year Of these 8 patients 3 gave indigestion as a symptom 2 nervousness and 3 angina pectoris Three others had complained of indigestion and nervousness for as long as four years 1 reported dyspnea for as long as five years The 52 remaining patients had noted some form of distress (angina pectoris in 38 cases) for less than one year in most cases for only a few months Three of the 38 who had had angina pectoris for less than a year had suffered tightness in the chest on exertion for only three days before the acute attack symptoms which may represent a partial occlusion of one of the coronary vessels progressing with continued activity to complete occlusion and infarction

It is noteworthy that only 4 of the 100 patients suffered no pain during the attack although they did have other complaints such as dizziness nausea and vomiting and so on (see Table 5) The pain when experienced lasted on the average, approximately six hours with extreme variations of from twenty minutes to seventy two hours

TABLE II–5 Symptoms at onset of acute episode of coronary heart disease for 100 patients (97 male and 3 female)

Symptom	No of patients
Chest pain (substernal and/or precordial)	96
Nausea	15
Indigestion	14
Dyspnea	10
Vomiting	8
Excessive sweating	8
Dizziness	5
Weakness	2
Cyanosis	2
Headache	1
Palpitation	1
Choking	1

The locations to which the chest pain radiated were not always the classical sites in less than half of the instances of radiated chest pain (29 out of 68 patients) did the pain radiate down both arms It is noteworthy that in 28 cases there was chest pain with no radiation These observations are summarized in Table 6

TABLE II–6 Radiation of pain during acute episode of coronary heart disease for 96 male patients*

Pain	No of patients
Radiation of pain to	68
both arms	29
left arm	17
left wrist and hand	11
left hand and fingers	9
middle of back	8
left shoulder	5
left elbow	4
upper abdomen	4
mandible and teeth	3
throat	2
right shoulder	2
right arm only	1
both clavicles	1
left ear	1
single radiation	39
multiple radiation (combinations of above)	29
No radiation of pain	28

* 4 patients (1 male and 3 female) did not experience pain

TABLE II–7 Activity at onset of acute episode of coronary heart disease for 100 patients (97 male and 3 female)

Activity	No of patients
Resting	22
Walking	21
Manual labor	18
Sleeping	11
Performance of professional duties	8
Exercising (calisthenics baseball)	6
Climbing steps	4
Driving or riding	3
Getting out of bed	3
Eating	2
Running	1
Dressing	1

Activity at onset of acute episode

The types of activity in which the individuals were engaged immediately prior to the acute episode are summarized in Table 7

Of the 18 patients listed as having their major attack while performing manual labor 9 experienced it while engaged in some type of work to which they were not accustomed In 2 of these cases unusual excitement superimposed on the unusual activity was perhaps an additional factor A total of 21 were engaged in some type of activity exercise or otherwise that required greater work on the part of the heart than was required by their usual daily routine It is believed that this may have been a factor in the devel opment of infarction of the myocardium at least in some patients *Of the 100 cases one third were resting or sleeping at the onset* of the acute myocardial infarction

Status and Clinical Findings at Initial Examination

Seventy of the patients had been hospitalized at the time of the acute myocardial infarction for an average of 6 2 weeks and had remained inactive following the hospitalization period for an aver age of three months Twenty-one patients had been treated at home for a similar period and 9 cases had gone unrecognized or ignored during the illness No attempt was made in this study to evaluate the methods of treatment that had been carried out during the acute illness

In the majority of cases the physical examination made for

the present study was remarkably unrevealing This observation is not new it is the experience of most physicians who have the opportunity to see cases of coronary heart disease after the initial acute episode

It was striking to observe in this group that the features of almost every individual appeared to be at least a decade older than his chronological age This raised the question that has been considered by Carrell and others How does the rate of living affect the longevity of the individual? The typical physique of coronary heart disease patients (discussed in Chapter IV) is associated with an energy expenditure that can be far greater than the expenditure of those with a more linear physique who do not usually experience the disease Are persons who experience coronary heart disease at a relatively young chronological age therefore, actually a decade older by physiological standards? This hypothesis has been suggested by Paul D White and Samuel A Levine in their various publications and lectures

Heart

In only 1 case was a murmur grade 3 apical systolic, considered of any consequence although a grade 1 apical systolic murmur was recorded in 7 other cases In all 8 cases the murmurs were found in hearts reported to be enlarged in the left ventricular component The aortic second sound was greater than the pulmonic second sound in 74 cases and P2 was greater than or equal to A2 in the remaining 26 cases

Abnormal jugular pulsations were found in 1 case accompanied by tachycardia and by gallop rhythm which was also heard in 3 other cases

Blood pressure

The highest systolic pressure recorded was 160 mm of mercury the highest diastolic pressure was 108 mm of mercury The average blood pressure for the entire group was 123 systolic and 81 diastolic The systolic and diastolic pressures exceeded 150 and 100 mm of mercury respectively in only 5 instances However only 1 patient could be classified as having hypertensive heart disease (at the time of examination his pressure was normal owing to a sympathectomy) It will be recalled that one of the criteria of selection



FIGURE II–1 X ray picture showing an aneurysm of the left ventricle apical portion

of patients for this study was the absence of hypertension This fact helps to explain the blood pressure findings

Fluoroscopic and x ray findings

During our initial examination 97 of the patients were studied by x ray consisting of both fluoroscopy and 7 foot chest films in the P–A view In addition left and right oblique views were taken in 10 cases In 39 instances the heart was enlarged as reported by the roentgenologists Even though the cardiothoracic ratio is an inaccurate means of determining the relative size of the heart this was computed in each case and in 22 instances the heart was found to be 50 per cent or more of the transverse diameter of the inner rib cage

Two cases were found of left ventricular aneurysm with paradoxical pulsations In 1 of these cases (see Figure 1) the infarction had occurred nine years previously in the other case only one year before Eight cases presented fluoroscopic evidence of diminished pulsations along the lateral margin of the left ventricle which the roentgenologists interpreted as being possible old areas of infarction with scarring This incidence is much lower than that reported by other authors (Dack et al)

Electrocardiographic findings

Using the three standard limb leads three unipolar limb leads (aVR aVL aVF) and six unipolar precordial leads (V1 to V6) evidence of infarction was demonstrable in every case including one of ten years duration and another of twenty one years duration This 100 per cent electrocardiographic confirmation is not surprising because in this study only those cases were selected which had an absolutely certain diagnosis There were 54 cases of anterior or anteroapical infarction as evidenced by QRS wave ST segment and T wave changes in standard limb leads 1 and/or 2 aVL and the precordial leads There were 40 cases of posterior or posterolateral infarctions as shown by alterations of QRS ST T complexes in standard limb leads 2 and/or 3 and lead aVF In the majority of individuals examined the septum was involved to some extent Six cases presented the electrocardiographic picture of both anterior and posterior infarctions The results are summarized in Table 8

TABLE II 8 Electrocardiographic findings in 100 patients (97 male and 3 female)

	No of patients
Distribution of myocardial infarction	
anterior or anteroapical site of infarction	54
posterior or posterolateral site	40
both sites	6
Disturbances of rhythm	
normal sinus rhythm	93
sinus tachycardia	3
sinus bradycardia	3
premature contractions (auricular)	1
paroxysmal tachycardia	0
auricular fibrillation or flutter	0
Conduction defects	
A V block—partial	2
A V block—complete	0
right bundle branch block	3
left bundle branch block	2
other impaired intraventricular conduction	2
no conduction defects	91
Axis deviation	
left ventricular hypertrophy	11
left axis deviation	14
right ventricular hypertrophy	0
right axis deviation	3
no axis deviation	72

Miscellaneous findings

ARCUS SENILIS Arcus senilis has been considered to be related to cholesterol metabolism, and it was stated by Boas (1945) that the incidence of arcus senilis increases with hypercholesterolemia This concept was later questioned and additional evidence was presented which did not support Boas thesis (Garn and Gertler 1950) In the present study only 5 patients had an arcus senilis The level of total cholesterol in their serum averaged 275 mg per cent

TOBACCO AND ALCOHOL The question of the effects of tobacco and alcohol on coronary heart disease and the possible relation between these two factors was considered in this study The results are summarized in Tables 9 through 12

It is evident that the coronary heart disease group smoked a few more cigarettes per day than did the unmatched control group These data however do not give any information on the effect of smoking on the cardiovascular system such as has been presented by several authors (Levy et al 1947 Evans and Stewart 1943

TABLE II–9 Daily tobacco use in coronary heart disease group of 90 males* and unmatched control group of 139 males† (Mean ± S E)

	Cigarettes smoked	*Ciga s smoked*	*Pipefuls‡ smoked*
Coronary group	19 4 ± 1 6	17 ± 10	85 ± 29
Control group	13 8 ± 1 1	25 ± 09	56 ± 16

7 patients did not respond to the questionnaire
†7 controls did not respond to the questionnaire
‡Each pipeful was considered to be 0 1 ounce

TABLE II–10 Smokers and non smokers in coronary heart disease group of 90 males* and unmatched control group of 139 males†

	SMOKERS		NON SMOKERS	
	No		*No*	%
Coronary group	81	90	9	10
Control group	107	77	32	23

7 patients did not respond to the questionnaire
†7 controls did not respond to the questionnaire

TABLE II–11 Weekly alcoholic consumption in coronary heart disease group of 92 males* and unmatched control group of 140 males† (Mean ± S E in ounces)

	Beer	*Wine*	*L quor‡*	*Total*
Coronary group	25 ± 4 87	2 9 ± 1 14	6 4 ± 1 27	34 3
Control group	32 ± 5 08	2 5 ± 0 56	3 6 ± 0 69	38 1

5 patients did not respond to the questionnaire
†6 controls did not respond to the questionnaire
‡Rye and scotch whiskey and gin

TABLE II–12 Consumers of alcohol in coronary heart disease group of 92 males* and unmatched control group of 140 males†

	CONSUMERS		ABSTAINERS	
	No	%	*No*	%
Coronary group	69	75	23	25
Control group	111	79	29	21

*5 patients did not respond to the questionnaire
†6 controls d d not respond to the questionnaire

English et al, 1940) It should not be inferrred from these results that cessation of smoking will necessarily benefit or prevent coronary heart disease

In Table 10 the smokers and non smokers in the unmatched control group and coronary heart disease group are considered Although it is evident not only that (*a*) the smokers in the coronary group smoked somewhat more than the smokers in the control group but that (*b*) there were proportionately more in the coronary disease group who smoked the difference seems to be unimportant

In Tables 11 and 12 two topics are considered (*a*) the amount of alcoholic beverage consumed by the two groups and (*b*) the number in each group who abstained from alcoholic beverages In Table 11 it will be seen that the coronary heart disease group ingested more liquor in the form of whiskey and gin But in total quantities the unmatched control group ingested more alcoholic beverages of all kinds i e 38 ounces to 34 ounces

In Table 12 it is evident that the difference between abstainers in both groups was insignificant

From this study no definite conclusions may be drawn as to the effects of alcohol on the development of atherosclerosis or on the precipitation of a myocardial infarction

BLOOD GROUPS Boyd (1950) has applied a genetic system of classification to man He bases his method on the hypothesis that the genes which determine blood groups do not differ fundamentally from the genes which affect morphological characteristics Such a system is necessarily limited by our understanding of the complex biochemical factors involved but it has nevertheless been established on a firm footing by Boyd Extending Wiener s proposal (1951) of racial classification by means of blood groups Boyd (1950) has suggested six racial divisions based on blood group differences

Since the refinements of Boyd s technique were unavailable in this study our data on blood groups and Rh factors cannot be employed with as great assurance as Boyd s data Nevertheless certain differences did exist even in this rough classification The control group had a larger percentage of Group O and of Group O with Rh positive than did the coronary heart disease group but a smaller percentage of Group A and Group A with Rh positive (see Table 13)

TABLE II–13 Blood groups Rh factors and combinations thereof in coronary heart disease group of 94 males* and unmatched control group of 145 males†

	CORONARY PATIENTS		UNMATCHED CONTROLS	
	No	%	No	%
Blood group				
A	37	46 0	51	35 2
B	14	17 2	21	14 4
AB	4	4 9	4	2 8
O	26	32 2	69	47 5
Rh factor				
positive	71	88 8	116	80 0
negative	9	11 2	29	20 0
Blood group and Rh				
A +	27	40 3	38	26 1
A —	4	5 9	13	8 7
B +	10	14 9	17	11 7
B —	0	0 0	4	2 7
AB +	3	4 5	3	2 1
AB —	1	1 4	1	7
O +	19	28 3	58	40 5
O —	3	4 5	11	7 6

For 3 of the 97 male coronary heart disease patients neither blood group nor Rh factor was recorded In the remaining group of 94 patients the blood group was not recorded in 13 cases and the Rh factor was not recorded in 14 other cases

†For 1 of the unmatched controls no data were recorded

Prognosis

At the time when this report was undertaken (December 1 1949) *10 patients in this series had died since examination* all apparently from recurrent infarctions 6 of these deaths occurred after one additional infarction 3 after two additional infarctions and 1 after three additional infarctions Twenty six others had suffered additional infarctions including 2 who had had a total of three infarctions and 1 a physician who had had a total of four infarctions but who still carried on a limited practice

Eighteen of the patients had not restricted their work or activity in any way and had no complaints referable to the cardiovascular system at that time Twenty four had voluntarily limited their work or exercise and likewise had no cardiovascular complaints One man was crippled by gout The remaining 57 patients had complaints of angina of effort dyspnea or a combination of complaints (see Table 14) Two were listed as heavy users of nitroglycerine 1 taking approximately 300 tablets per week

The 90 living patients had survived an average of 3 92 years

TABLE II–14 Symptoms in 1949 of the 90 living patients with previous myocardial infarction

Symptoms	No of patients
Angina pectoris	36
Dyspnea	16
Palpitation	9
Fatigue	4
Dizziness	2
Crippled by gout	1
Limitation of activity without specific complaints	24
No complaints	18

from the date of the acute episode until this report One man was alive 22 5 years after the original episode though crippled by gout at this time The 10 patients who had died since our original examination had survived an average of 3 5 years including 1 who had remained alive and active for over 11 years Eight of the 10 who died had had preceding complaints for from two months to as long as five years consisting of mild to severe dyspnea and angina pectoris associated principally with effort Thirty six patients who had complaints before infarction such as angina pectoris dyspnea or palpitation continued to have these same complaints frequently to a more severe degree afterwards

There were 16 who listed some complaints before infarction who at the time of writing were free of symptoms However it must be remembered that the majority of these patients had markedly curtailed their activities and did not extend themselves to the point of inducing angina pectoris dyspnea or other symptoms

Summary

The findings discussed in this chapter leave little doubt that pure coronary heart disease (that is uncomplicated by hypertension xanthomatosis diabetes or nephrosis) is predominantly a male disease prior to the age of 40 The patients in this study in all instances revealed prodromal symptoms varying from direct cardiac symptoms such as chest pain (both precordial and substernal) to seemingly unrelated symptoms such as indigestion or headache However it is noteworthy that in 96 per cent of the patients the symptoms were referable to chest pain There appeared to be a relation between season of the year and infarction, for 60

per cent of the acute episodes occurred during a 5 month period between November 1 and March 30 The use of alcohol and of tobacco was greater in the coronary heart disease group but the differences were not sufficient to imply a causal relation

The 97 men in the coronary group appeared about a decade older than their chronological stated age Aside from this clinical observation there were no other striking clinical phenomena Only 2 instances of left ventricular aneurysm and only 10 instances of diminished or paradoxical pulsation were observed during fluoro scopic examination The heart sounds and the electrocardiograms did not reveal any unusual or definitive diagnostic features Blood studies either by groups or Rh factors did not reveal any sug gestive clues as to genotypes or phenotypes in coronary heart disease

REFERENCES

BOAS E P Arcus senilis and arteriosclerosis *J Mt Sinai Hosp* 12 79–83 1945

BOYD W C Use of blood groups in human classification *Science* 112 187–196 1950

DACK S SUSSMAN M L and MASTER, A M Roentgenkymogram in myocardial infarction clinical and electrocardiographic correlation *Am Heart J* 19 464–474 1940

ENGLISH J P WILLIUS F A and BERKSON J Tobacco and coronary disease *J.A.M.A* 115 1327–1329 1940

EVANS W F and STEWART H J The effect of smoking cigarettes on the periph eral blood flow *Am Heart J* 26 78–91 1943

GARN S M and GERTLER M M Arcus senilis and serum cholesterol levels in the Aleut *New England J Med* 242 283–285 1950

GLENDY R E LEVINE S A and WHITE P D Coronary disease in youth com parison of 100 patients under *40* with *300 persons past 80 J.A.M.A 109 1775–*1781 1937

GORDON W H BLAND E F and WHITE P D Coronary artery disease analyzed post mortem with special reference to the influence of economic status and sex *Am Heart J* 17 10–14 1939

HERRICK J B Clinical features of sudden obstruction of the coronary arteries *J.A M.A* 59 2015–2020 1912

HOOTON E A Personal communication

LEVY R L MATHERS J A L MUELLER A A and NICKERSON J L Effects of smoking cigarettes on the heart *J.A.M A* 135 417–422 1947

WIENER A S Rh–Hr blood types serology genetics and nomenclature *Tr N Y Acad Science* 13 199–205 1951

YATER W M TRAUM A H BROWN W G FITZGERALD R P., GEISLER, M A and WILCOX B B Coronary artery disease in men eighteen to thirty nine years of age *Am Heart J* 36 334–372 1948

CHAPTER III

Family Incidence The Role of Heredity and Race

In clinical practice coronary heart disease is not infrequently encountered in siblings and cardiologists who have been established for some years often have treated both father and son Such observations have led to the conclusion that coronary heart disease is a *familial* disease that it runs in families Some fairly impressive material has been published to support this contention (Musser and Barton 1931 Gates 1946)

It has also been observed that patients with coronary heart disease often come from short lived families from families showing other cardiovascular disorders or from families with diabetes renal disease and/or other degenerative diseases These observations would suggest in turn either that the life span of the parents of the patients was shortened by coronary heart disease (though not necessarily diagnosed as such) or that the factors for the development of the disease were pleiotropic in character and diseases of the coronary arteries were one expression of the general syndrome

Clinicians have also noted that in this country Jews seemingly have a high while Negroes have the lowest incidence of coronary heart disease (Yater et al 1948) Such observations together with tentative reports from other countries suggest that there is a racial factor involved

When these observations are taken together—the facts that the disease appears to be familial that it is associated with a shortened life span in the parents of patients and that there appear to be racial variations in the incidence of the disease—it is reasonable to suspect the existence of hereditary genetic factors in the etiology of coronary heart disease This being so the next step is to attempt to uncover these factors

TABLE III–1 Survival of parents of coronary heart disease group of 97 males and unmatched control group of 146 males

	PARENTS OF CORONARY GROUP		PARENTS OF CONTROL GROUP	
	No	%	*No*	%
Mothers	97	100	146	100
living	56	58	107	73
dead	41	42	39	27
Fathers	97	100	146	100
living	32	32	65	45
unknown	3	4	5	3
dead	62	64	76	52
Total parents	194	100	292	100
living	88	45	173	59
unknown	3	2	5	2
dead	103	53	114	39

Family Mortality and Average Length of Life

Method

During the course of the interviews both the patients and the 146 controls were questioned about the physical condition of their parents grandparents and siblings whether they were living and if not the cause of death (if known) The data obtained from these interviews (see Appendix B) were compared with those obtained from detailed written questionnaires filled out by each individual subsequent to the interview thus duplicate records were obtained for both the patients and the controls Discrepancies between the two records were resolved by further communication with the subjects or with referring physicians or by recourse to hospital records or to relatives of the patients In cases of doubtful information or questionable reports no entries were made

From the final records master genealogical charts were drawn up for both groups (see Appendix C) and from these master charts the final tabulations were computed It should be noted that these tabulations represent the situation at the time of the final interview

Frequency and cause of death among parents

Table 1 gives the number and proportion of parents who were living or dead at the time of the final interview It shows that the proportion of parents living at the time of the final interview was higher in the unmatched control group than in the patient group

TABLE III-2 Mean age of parents at time of death * unmatched control group and coronary heart disease group

	PARENTS OF CORONARY GROUP		PARENTS OF CONTROL GROUP		*Difference*
	No	*Age in years*	*No*	*Age in years*	*years*
Mothers	39†	55 6 ± 2 08	35‡	59 0 ± 2 10	4 4
Fathers	61§	58 8 ± 1 54	72‖	59 7 ± 1 60	0 9
Difference		3 2		0 7	

*For a total of 11 parents the age at death was not known hence the totals are smaller than in Table 1

†2 mothers ages at death were unknown

‡4 mothers ages at death were unknown

§1 father s age at death was unknown.

‖4 fathers ages at death were unknown

Of the mothers of 146 controls 73 per cent were alive as compared with 58 per cent of the patients mothers Similarly 45 per cent of the fathers of the controls were alive as compared with 32 per cent of the fathers of the patients For total parents 59 per cent of the parents of the controls were alive as compared with 45 per cent of the parents of the patients Since these differences are statistically significant it is concluded that mortality is higher among the parents of the 97 male patients

In order to determine whether the difference in mortality could be attributed to a difference in the age distribution of the two groups of parents the ages of the surviving parents at the time of the final interview were compared The surviving mothers of the control group and patient group respectively averaged 63 9 years and 64 4 years the fathers averaged 66 4 years and 66 0 years The slight differences of 5 year and 4 year were too small to be significant Hence the different mortality cannot be attributed to an age difference

The average ages at death of mothers and fathers of the coronary heart disease patients and the controls are compared in Table 2 It will be noted that the averages for the coronary heart disease group were in each case somewhat less than for the control group This might have been anticipated in view of the higher percentage of dead parents in the coronary heart disease group (see Table 1) However this difference in the average age at death of the parents in both groups is not statistically significant It will also be noted that the average age at death of the mothers was somewhat less (although not significantly) than that of the fathers in both groups

This is in keeping with statements by Eppinger and Levine (1934) who suggested that the parents of patients with angina pectoris show a somewhat lower mean age at death than the general population and that the patients mothers die at an earlier age than their fathers

Since a higher proportion of the patients than of the controls parents were deceased it was of interest to compare the causes of death As shown in Table 3 the deceased parents of the patients showed a higher percentage of deaths attributable to disease of the cardiovascular system and fewer deaths attributable to certain other causes

Of the deceased mothers 51 3 per cent in the patient group died of cardiovascular disorders of all kinds as compared with 35 9 per cent in the control group Of the deceased fathers 64 6 per cent in the patient group died of cardiovascular defects of all kinds as compared with 46 2 per cent in the control group

The patients fathers showed a larger proportion of deaths due to disease of the coronary arteries 37 1 per cent of those deceased as compared with 18 5 per cent of deceased fathers of the control group The difference is significant There was practically no difference in the percentage of deaths from disease of the coronary arteries among the mothers of the two groups 9 8 per cent in the coronary group and 7 7 in the control group

Naturally certain questions arise as to the validity of these findings While the results given here are derived at first hand from personal interviews and questionnaires *all* the information stems from the same source and is subject to bias or error by the individual It is quite possible that a patient might give retrospective diagnosis —that is assume that the parent necessarily died of the disorder that is a source of concern to the patient himself However it should be pointed out that the proportions of deaths said to be due to old age unknown causes accident and so forth are comparable in the two groups

Bearing these cautions in mind the data suggest then that the parents of coronary disease patients show a high proportion of deaths due to disorders of the heart and circulation and that much or all of the excess may be due to diseases of the coronary arteries While this in itself does not confirm the factor of inheritance it is extremely suggestive

TABLE III-3 Cause of death for parents and siblings of coronary heart disease group of 97 males and unmatched control group of 146 males

Cause of death	Coronary group: Mother No	%	Father No	%	Siblings No	%	Control group: Mother No	%	Father No	%	Siblings No	%
Diseases of the coronary arteries	4	9.8	23	37.1	5	8.6	3	7.7	14	18.5	1	1.0
Other cardiovascular diseases	17	41.5	17	27.5	11	19.0	11	28.2	21	27.7	7	7.2
Total cardiovascular diseases	21	51.3	40	64.6	16	27.6	14	35.9	35	46.2	8	8.2
Cancer and other neoplasms	5	12.2	3	4.8	2	3.4	5	12.8	7	9.2	4	4.1
Diabetes mellitus	1	2.4	1	1.6	2	3.4	1	2.6	2	2.6	1	1.0
Renal diseases	1	2.4	1	1.6			2	5.1	3	3.9	2	2.0
Anemia (pernicious)									1	1.3		
Liver diseases							1	2.6				
Diseases of infancy (various)					15	25.9					44	44.9
Influenza and pneumonia	5	12.2	8	12.9	3	5.2	4	10.3	6	7.9	2	2.0
Tuberculosis (all forms)					5	8.6	2	5.1	5	6.6	3	3.1
Infections (scarlet fever diphtheria mastoiditis meningitis)	1	2.4			5	8.6	3	7.7	1	1.3	6	6.1
Syphilis			1	1.6								
Alcoholism									1	1.3		
Neurological (epilepsy paralysis agitans)			1	1.6	2	3.4			1	1.3		
Violence and accident	2	4.9	4	6.5	6	10.4	2	5.1	6	7.9	16	16.3
Miscellaneous and unknown	5	12.2	3	4.3	2	3.4	5	12.8	8	10.5	12	12.2
TOTAL	41		62		58		39		76		98	

Sex ratios among siblings

Since some disorders are characterized by a disproportionate sex ratio apparently due to factors that act as lethal in one sex and as semilethal in the other it was of interest to study the sex ratios of the siblings These were calculated for all 100* patients and the 146 male controls The *young coronary patients had 388 siblings* (not counting those stillborn whose sex is unknown) Of this 388 total 53 per cent were males In the control group there were 482 siblings of whom 246 or 51 per cent were males The ratio of males to females does not depart significantly from the theoretical 1 06 1 nor do the ratios in the two groups differ significantly From the total number of siblings it was calculated that the average numbers of children in a patient s and in a control s family were 4 88 and 4 30 respectively

Although the patients and controls may not yet be considered to have completed their own families the average numbers of offspring at the time of the final interview were 1 77 and 1 70 respectively The ratios of male to female children were 0 85 1 0 and 1 03 1 0 It is obvious that these differences are not significant

Frequency and cause of death among siblings

Since the parents of the patients showed a higher mortality and a larger proportion of deaths attributable to the heart and vascular system it was of interest to compare the siblings of the patients and the controls in this respect Of the 482 siblings of the 146 control subjects 98 or 20 per cent had died up to the time of the interviews Of the 388 siblings of the 100 patients 58 or 15 per cent had died up to the time of the interview The difference in mortality is not significant

The causes of death however show a marked difference between the two groups As shown in Table 3 the deceased siblings of the coronary patients showed an excess of cardiovascular disorders Of the 58 deceased siblings of the young coronary patients 27 6 per cent died of various cardiovascular disorders as contrasted with 8 2 per cent of the deceased siblings of the control group this difference in percentage is significant Much of the difference is due to the higher coronary heart disease rate among the siblings

Since the results are not affected by the sex of the proband (or index patient) it was allowable to include both the 97 males and the 3 females in this tabulation

TABLE III-3 Cause of death for parents and siblings of coronary heart disease group of 97 males and unmatched control group of 146 males

Cause of death	CORONARY GROUP						CONTROL GROUP					
	Mother		Father		Siblings		Mother		Father		Siblings	
	No	%	No	%	No	%	No	%	No		No	%
Diseases of the coronary arteries	4	9.8	23	37.1	5	8.6	3	7.7	14	18.5	1	1.0
Other cardiovascular diseases	17	41.5	17	27.5	11	19.0	11	28.2	21	27.7	7	7.2
Total cardiovascular diseases	21	51.3	40	64.6	16	27.6	14	35.9	35	46.2	8	8.2
Cancer and other neoplasms	5	12.2	3	4.8	2	3.4	5	12.8	7	9.2	4	4.1
Diabetes mellitus	1	2.4	1	1.6	2	3.4	1	2.6	2	2.6	1	1.0
Renal diseases	1	2.4	1	1.6			2	5.1	3	3.9	2	2.0
Anemia (pernicious)									1	1.3		
Liver diseases							1	2.6				
Diseases of infancy (various)					15	25.9					44	44.9
Influenza and pneumonia	5	12.2	8	12.9	3	5.[illegible]	4	10.3	6	7.9	2	2.0
Tuberculosis (all forms)					5	8.6	2	5.1	5	6.6	3	3.1
Infections (scarlet fever diphtheria mastoiditis meningitis)	1	2.4			5	8.6	3	7.7	1	1.3	6	6.1
Syphilis			1	1.6								
Alcoholism									1	1.3		
Neurological (epilepsy paralysis agitans)			1	1.6	2	3.4			1	1.3		
Violence and accident	2	4.9	4	6.5	6	10.4	2	5.1	6	7.9	16	16.3
Miscellaneous and unknown	5	12.2	3	4.3	2	3.4	5	12.8	8	10.5	12	12.2
TOTAL	41		62		58		39		76		98	

TABLE III–4 Frequency of coronary heart disease in parents of coronary heart disease group of 100 (97 males and 3 females) and of unmatched control group of 146 males

	CORONARY GROUP		CONTROL GROUP	
	No of parents	*% of 00 total parents*	*No of parents*	*% of 29 total parents*
Father only	23		14	
Mother only	1		3	
Both parents	6*		0	
TOTAL	30	15 0	17	5 8

*3 pairs of parents

As described in the previous sections the genealogies which are given individually in Appendix C were analyzed in order to determine whether the mode of inheritance followed any simple genetic model The genealogies for the 146 control subjects are also included since they serve as an indication of the frequency of coronary heart disease in the parents of individuals of comparable age who were at the time of examination free from coronary heart disease The findings are tabulated in Table 4 The genealogies may be less than conclusive because the life experience with respect to coronary heart disease is not yet complete

In 73 of the 100 coronary heart disease cases *neither* parent exhibited the disease so far as is known In only 3 cases did *both* parents have the disease These 3 mothers plus 1 other whose hus band did not have the disease were the only 4 mothers said to have had it whereas a total of 26 of the fathers were said to have suffered from it

Five out of 58 or 8 6 per cent of the siblings of the coronary patients experienced coronary heart disease whereas only 1 out of 98 or 1 per cent of the siblings of the unmatched controls had coro nary heart disease The difference is statistically significant

For 131 of the 146 controls *neither* parent was said to have had coronary heart disease In no case were *both* parents of controls affected There were 3 mothers with a history of the disease—almost the same number as in the patient group Only 14 fathers were affected however compared with 26 fathers of patients

The incidence of the disease then is significantly greater in the parents of our patients (15 0 per cent) than in the parents of controls (5 8 per cent)

The proportion of males to females among the parents who

had had coronary heart disease varied in the two groups for the patients parents it was 26 4, or 6 5 1 and for the controls parents it was 4 7 1 The difference between these two ratios is large but in view of the small numbers of parents affected it is not statistically significant The larger number of males in both ratios is in keeping with the general observation that this is a predominantly male disease

The genealogies are interesting in that they fail to show a spectacular number of family members with coronary heart disease While Herapath and Perry (1930) Coombs (1930) and Boissevain (1931) have all described families with one affected parent and many affected siblings such family lines are probably exceptional cases and may be due to chance * In the present study even though all the family lines in the patient group were selected on the basis of one or more affected individuals few genealogies replete with coronary heart disease are found † The genealogy of Patient No 18 (Appendix C) shows 7 siblings 5 male and 2 female of whom 3 males were affected The father was also affected The genealogy of Patient No 26 shows an affected mother and 2 affected siblings out of 4 But genealogies with many affected siblings are absent, though this may well be attributable in part to the relatively low age of the group Similarly the control series fails to evidence family lines of the type described by Boissevain (1931) and by others

From the data it would appear to be highly unlikely that the disorder is inherited either as a simple Mendelian dominant or as a dominant covert in the female The proportion of affected fathers of patients (26 out of 100 fathers) is too small to fit either mode of inheritance ‡

The possibility that the disorder was inherited as a Mendelian recessive was checked further by examining the 3 cases in which both parents were affected If the disease was so inherited then both parents would be homozygous for the disorder and all the offspring would be affected But in these 3 cases among 20 siblings of affected patients there were no clear cases of coronary heart

*See Allan (1933)

†Coronary heart disease was a relatively rare diagnosis forty years ago and was doubtless often missed

‡If it were either a sex influenced, a sex limited or a simple dominant inheritance approximately 50 per cent of the fathers would be expected to show the disease assuming high penetrance

disease It is therefore highly unlikely that the disorder is inherited as a simple Mendelian recessive

The evidence is thus against the possibility of a simple mode of inheritance for coronary heart disease either as a dominant or as a recessive even considering its masked nature in the female However the data do suggest that the disease is familial (as witness the higher incidence of the disease in the parents and siblings of the patients) The most definite statement that can be made is that the disorder runs in families possibly a multiple factor condition with at least one dominant factor

Findings on Race

The statement has often been made that coronary heart disease has an unusually high incidence in one racially distinct group or an unusually low incidence in another With this in mind the ethnic origins of each coronary patient were analyzed in detail including the nationality of both parents (see categories in Table 5) and their place of birth as well as his own

TABLE III-5 Nationality categories of coronary heart disease group*

Group	*Symbol*	*Description*
1 Old American	A	Primarily northwestern European mixture resident in the North American continent for three or more generations (Hrdlicka 1925)
2 Austrian	Au	
3 Armenian	Ar	
4 Belgian	Be	
5 British Isles	B	A mixture of English Scotch Irish.
6 Danish	D	
7 English	E	Primarily second and third generation *English*
8 French	F	
9 French Canadian	FC	
10 German	G	
11 Irish	I	Primarily second and third generation Irish.
12 Italian	*I*	
13 *Jewish*	*J*	Primarily a blend of eastern Mediterranean racial elements forming an endogamous group (Coon 1939)
14 Portuguese	P	
15 Negro	N	Primarily a Gold Coast-Slave Coast blend usually with *Groups 1 and 5*
16 Syrian	S	

* There were no individuals of "pure" Scotch, Welsh Swedish, or Chinese origin, or of other national ties not included in the table

TABLE III–6 Nationality of parents of coronary heart disease group of 100 (97

	MATERNAL NATIONALITY						
PATERNAL NATIONALITY	*Old American* (*A*)	*Austrian* (*Au*)	*Armenian* (*Ar*)	*Belgian* (*Be*)	*British Isles* (*B*)	*Danish* (*D*)	*English* (*E*)
Old American (A)	15				1		
Austrian (Au)		1					
Armenian (Ar)			1				
Belgian (Be)				1			
British Isles (B)					9	1	
Danish (D)						1	
English (E)							4
French (F)							
French Canadian (FC)							
German (G)							
Irish (I)							
Italian (*I*)							
Jewish (*J*)							
Portuguese (P)							
Negro (N)							
Syrian (S)							

The findings of this survey of ethnic origin are summarized in Table 6 As would be expected from the make up of the general population in their area nearly half of the patients were derived recently or remotely from the British Isles 9 were pure British Isles 4 were pure English and 12 were pure Irish The Irish well represented in the urban populations of the northeast, are also well represented in the present series

Fifteen patients were 'old Americans' (following the definition by Hrdlicka 1925 see Table 5) Two of the group of 100 patients were Negroes Both were born in the South and sent to us from there no conclusion may be drawn from this fact however since it may merely reflect the source of the data

Of the 100 patients 27 were Jews (26 men and 1 woman), 1 was Syrian and 1 was Armenian As compared either with the general American population where the proportion of individuals ultimately derived from the Near East is approximately 6 per cent or with the urban Boston population where it approaches 14 per cent this 29 per cent is highly significant That the high ratio exists is general knowledge (Boas 1949) One may question whether the

males and 3 females)

				MATERNAL NATIONALITY				
French (*F*)	*French Canadian* (*FC*)	*German* (*G*)	*Irish* (I)	*Italian* (*I*)	*Jewish* (*J*)	*Portuguese* (*P*)	*Negro* (*N*)	*Syrian* (*S*)
			1					
3		1	2					
1		1						
1		1	1					
	1							
		2	1					
			12	1				
				6				
					27			
						1		
							2	
								1

excess represents an artifact of sampling or a real difference in incidence due to genetic or cultural factors In the series of previous investigators it has been questioned whether an excess of Jewish patients was due to a higher incidence of coronary heart disease or to a culturally conditioned drive to visit the top doctor In the present series it is unlikely that such patterned behavior was responsible for the excess since the 100 patients represent not the private practice of one physician but the private and ward practices of a large number of physicians spread out over a large area as well as patients obtained through hospital records the Veterans Administration and other sources

Summary

Clinical impressions favor the opinion that coronary heart disease is a familial disease There has however been little scientific documentation of these clinical impressions and since their implications are of the utmost importance for the control of the disease it was believed necessary to carry out studies in this area Obviously only a very close follow up study of hundreds of families over

several generations will provide a definitive analysis However, this study, which is cross sectional rather than longitudinal, did uncover certain clues and it is hoped that by a further follow up of both patients and controls more information will be obtained

Since coronary heart disease is encountered often in young men it was reasoned that the patients might come from short lived families and therefore a survey of the ages of parental deaths was made If in addition it was demonstrated that more parents of patients than of controls died of coronary heart disease then it could reasonably be suggested that this is a familial disease It was shown that more of the mothers and fathers of the coronary than of the control group were dead The differences in age at time of death were not statistically significant but it was shown that 37 1 per cent of the fathers in the coronary group compared with 18 5 per cent of the fathers in the control group died from coronary heart disease There was no significant difference in the percentages of deceased mothers (9 8 per cent and 7 7 per cent respectively), a fact that is not surprising since coronary heart disease is a male disease and is rarely experienced by women until after the menopause When however the data on other cardiovascular ailments were added to those for coronary heart disease it was clearly demonstrated that the death of both parents from some kind of cardiovascular disease was more common in the coronary group than in the control group (see Table 3)

As a further test for the thesis that coronary heart disease is a familial disease the cause of death of siblings of the coronary group was studied Here it was found that 8 6 per cent of the siblings of the coronary group as opposed to 1 0 per cent of the siblings of the control group died from coronary heart disease

On the basis of the evidence concerning the proportion of deaths and the causes of death in the parents and siblings of both groups it is reasonable to conclude that coronary heart disease is more likely to occur in families or individuals if mother father or siblings have experienced the disease

A problem which requires further work is the delineation of the hereditary pattern which predisposes to coronary heart disease A follow up report on the status of the patients and unmatched controls at the end of 1953 is presented in Appendix F

This chapter also considered racial susceptibility or immunity

to coronary heart disease Since the actual number of cases studied was not great specific conclusions pertaining to the general American population cannot be made It may be noted however that there were in this group of patients a preponderance of Jewish individuals and a scarcity of Negroes

REFERENCES

ADLERSBERG D Hypercholesteremia with predisposition to atherosclerosis in born error of lipid metabolism *Am J Med* 11 600–614 1951

ALLAN W Heredity in hypertension. *Arch Int Med* 52 954–958 1933

BAUER, J *Constitution and Disease* 2nd Ed Grune & Stratton, New York, 1945

BOAS E P *Coronary Artery Disease* Year Book Publishers Chicago 1949

BOISSEVAIN E The inheritance of angina pectoris *Eugenical News* 16 115 1931

BOYD W C Use of blood groups in human classification. *Science* 112 187–196 1950

COOMBS C F Observations on the aetiological correspondence between anginal pains and cardiac infarction *Quart J Med* 23 233–240 1930

COON C S *Races of Europe* Macmillan Co New York, 1939

COON C S GARN S M and BIRDSELL, J B *Races A Study of the Problems of Race Formation in Man* C C Thomas Springfield Ill., 1950

EPPINGER, E. C., and LEVINE S A Angina pectoris *Arch Int Med* 53 120–130 1934

GATES R. R. *Human Genetics* 2 vols Macmillan Co New York, 1946

HERAPATH C E K. and PERRY C B Coronary arteries in case of familial liability to sudden death *Brit M J* 1 685–687 1930

HOOTON E A *Up from the Ape* Rev Ed. Macmillan Co., New York, 1946

HRDLICKA, A *The Old Americans* Williams and Wilkins Co Baltimore 1925

LEVINE S A and HINDLE J A. Coronary artery disease among physicians *New England J Med* 233 657–659 1945

MUSSER, J H and BARTON J C The familial tendency of coronary disease *Am Heart J* 7 45–51 1931

SMYTH C J., COTTERMAN C W and FREYBERG R. H The genetics of gout and hyperuricemia an analysis of nineteen families *J Clin Investigation* 27 749–759 1948

SNYDER, L H *The Principles of Heredity* 3rd Ed D C Heath, Boston, 1946

STERN C *Principles of Human Genetics* W H Freeman and Co San Francisco 1949

WIENER A. S Recent developments in knowledge of Rh Hr blood types tests for Rh sensitization (Ward Burdick lecture) *Am J Clin Path* 16 477–497 1946

YATER, W M TRAUM A H., BROWN W G FITZGERALD R. P., GEISLER, M A., and WILCOX B B Coronary artery disease in men eighteen to thirty nine years of age *Am Heart J* 36 334–372 481–526 683–722 1948

CHAPTER IV

Anthropometric and Morphological Appraisal of Physique

ASSOCIATIONS real or imagined between type of physique and cause of death have been claimed for many years, but despite the persistence of these claims specific correlations have remained undemonstrated The robust pyknic physique has been more associated with cardiovascular disorders and the linear, asthenic type with respiratory disorders but individual predictions are hardly practicable (Sheldon 1940 Lessa 1943 Ciocco 1936 Bauer, 1945 Petersen, 1932)

On the other hand actuarial and biometric studies employing large numbers of individuals have all demonstrated that cardiovascular disorders are more frequent in individuals who are above normal weight than among those who are below normal weight This general relation however is less well demonstrated in the female than in the male (Dublin and Marks 1938) and, even in the male the more carefully the physique is defined the less perfectly the generalization is maintained

As these authors showed (1937) the mortality of tall overweight men is greater than that of short overweight men while the mortality of tall overweight men with short spines is far greater than that of tall overweight men with long spines Thus within the general group of overweight' men certain physiques have a mortality over expectancy while other physiques still overweight' have no excess mortality Pearl (1940) and Pearl and Ciocco (1934) also show that the more precisely a physique is defined the better the differentiation between disease groups Thus in the present study the problem is to define the factors of physique and morphological character as sharply as possible in order to obtain optimum differentiation between those with specific disease predispositions and others not so predisposed

Studies by Other Investigators

Since coronary heart disease has been recognized only rather recently as a disease of the younger adult and since such cases are infrequent in the private practice of any one cardiologist descrip tions of the physique of the patients as a group have come in recent years only although many individual cases have been reported

Levine and Brown (1929) commented that young office patients with coronary heart disease had round thick wrists and other char acteristics suggesting both musculature and rotundity The first survey of coronary heart disease in young individuals made by Glendy et al (1937) included a brief summation of physique According to their study which employed standards not defined the majority of these young patients were either obese or over weight only 30 per cent were average or lean French and Dock (1944) in a preliminary study of coronary heart disease in young soldiers also reported that the majority of 80 initial cases were overweight or obese The same trend was observed in a study by Goldsmith and Willius (1937) who found that in com parison with insurance company standards a group of patients who had experienced coronary thrombosis were significantly over weight Similarly McCain et al (1950) reported that 23 per cent of 281 autopsied cases of myocardial infarction were obese On the other hand Yater et al (1948) reporting on a very extensive Army series including French and Dock s 80 cases noted that the men who died ultimately after experiencing verified coronary athero sclerosis with infarction were often overweight at the time of in duction but not at the time of death This important observation questioned the role of weight per se in the etiology of coronary heart disease and also raised the problem of whether weight reduc tion constituted any real preventive therapy Moritz and Zamcheck (1946) similarly showed that Army men who died after coronary occlusion were no heavier than Army men who died accidental deaths although both groups were overweight" if norms based on inductee statistics were used This explained the findings of French and Dock (1944) while at the same time questioning the validity of the conclusions in earlier studies Overweight alone did not seem to be the factor

White (1944) on the other hand following Levine and Brown (1929) stressed as an etiological factor not fat or obesity but

rather the fact that many of his young male coronary patients were well muscled athletic and in a sense, the 'most masculine of men suffering at an unusually early age a highly sex limited disorder Newman (1946) observed the same physique factor in his British Army study the soldiers who developed coronary heart disease were fine physical specimens and ranked high on physical fitness scores

Thus various studies did suggest a physique factor in the etiology of coronary heart disease but the actual description of the physique was not formulated Despite this lack of agreement in the studies themselves most clinicians have assumed that fat is an etiological factor in coronary heart disease and have employed weight reduction for therapy

It was one of the purposes of the present study to investigate the physique of individuals who had experienced myocardial infarction from the standpoint not only of habitus and anthropological type but also of masculinity of build since it had been suggested by Draper (1941 1944) Seltzer (1945) Sheldon (1940 1949) and others that disorders with a higher incidence in the male are often more common in hypermasculine than in hypomasculine physiques The basic problems for investigation then, were

1 What physique distribution actually exists among individuals who have coronary heart disease at an early age?
2 Is obesity a prime etiological factor in this disorder?
3 Is there a coronary physical type?

Method of Appraisal in Present Study

The suggestions inferences and clinical hunches about the physical characteristics of the young male with potential coronary heart disease led to the formulation of a program designed to embrace most of these leads The program of physical appraisal was set up to investigate (*a*) the anthropometric characteristics of the coronary group determined by standard measurements (*b*) weight in the coronary group its relation both to accepted standards and to the weight of a comparable group of healthy males as well as coronary weight height ratios (*c*) the gross morphological character of the coronary patients in terms of physique habitus or body build

These programs of investigation were carried on by the methods

of investigative research used by physical anthropology Weight and height weight data were gathered and subjected to analysis Physique ratings were given first at the time of examination and later in revised form after inspection of standardized somatotype photographs which permit the simultaneous inspection of three views of the individual at once Measurements were taken and studied and indices of proportions were calculated with a special view to obtaining a description of the thoracic region Morphological traits were selected among the hundreds available to include such features of age as balding and graying such features possibly correlated with masculinity or virility as total hairiness and specific features relating to the configurations of the pectoral region the waist the hips and the thighs Moreover other data possibly related to masculinity were included among the ratings (see Chapter VI) The problem of assessing masculinity objectively is an inordinately difficult one Voice pitch and size of genitalia were noted but were not thought satisfactory for objective recording

In all there were 24 measurements regularly made in addition to age 12 indices were used in the final report and 32 additional characteristics and morphological traits were rated (see Seltzer 1943 and Kovacs and Hartnung 1935 who also used anthropometry in the study of a disease population)

These individual ratings and measurements were separately related to the psychological hormonal biochemical and physiological studies in progress The physical appraisal in the anthropological sense is considered in this chapter while the detailed considerations of the findings and their interrelations with other data are considered separately in this monograph and in other publications Because of the probable unfamiliarity of the medical profession with the anthropometric methods involved they are presented in somewhat greater detail than they would have been in a report designed simply for an anthropological audience These findings must be confirmed or refuted in terms of the methods employed Were they not given in sufficient detail to allow other workers to test their reliability * it would be difficult to appraise their value satisfactorily

* Reliability is here used in the sense employed in psychological testing A reliable test is one that consistently produces the same results in the hands of different observers who employ the same methods An "unreliable" test is one that may be internally consistent only in the hands of the same observer

Anthropometric Findings

Measurements and indices used

In selecting measures for this study we desired contact measurements as close to the skeletal measurements as possible (so that there would be less age influence) as well as measures of both central mass and thoracic mass In this way we could determine whether differences were (*a*) general, (*b*) concentrated in the thoracic trunk or (*c*) peripheral In addition we desired to test specifically the alleged obesity of coronary heart disease patients by comparing the measurements of waist breadth and hip breadth assuming that abdominal flaccidity is the best single measure of this ill defined term obesity

In addition to general measures we selected a few that show little variation with physique but do show racial differences Thus it was possible to use race influenced measures as indicators of possible sampling errors

The measurements of the thoracic trunk were four in number chest depth (upper) chest depth (lower) chest breadth and chest length (sternum ensiform) There were four measurements of the peripheral region hand length hand breadth wrist depth wrist breadth Ten measurements of the head and face were taken bi pupillary nose length nose breadth upper face length, total face length biocular bizygomatic bigonial head breadth and head length

Girths were not used because of the difficulties in determining the proper point of measurement in an older and usually plumper population

MEASUREMENTS

Abbreviations
A = Anthropometer
S C = Sliding Caliper
Sp C = Spreading Caliper

Starred items are standard for anthropometric measurements (Hooton 1946 Martin 1928) Metric measures were used except for weight which was recorded in pounds

1 *Age to past birthday
2 *Weight nude or with minimum clothing
3 Usual weight average weight in five years previous to exam ination as stated by the subject
4 *Stature maximum height to vertex
5 Span tip to tip arms fully extended A
6 *Shoulder breadth biacromial taken from the front A
7 *Chest breadth chest breadth at level of nipple moderate pres sure A
8 Waist breadth waist minimum contact measurement A
9 *Hip breadth bi iliac A
10 Upper chest depth midmanubrium to spine anthropometer level A
11 *Lower chest depth sternum to spine at level of nipple mod erate pressure A
12 Chest length (sternum ensiform) sternal notch to palpated bony tip of xiphoid process A
13 *Bipupillary interpupillary diameter with eyes relaxed S C
14 *Nose length nasion (by projection) to subnasale S C
15 *Nose breadth maximum bialar S C
16 *Upper face length nasion (by projection) to prosthion (by projection) S C
17 *Total face length nasion (by projection) to menton (mod erate pressure) S C
18 Wrist breadth distal tuberosity of radius to distal tuberosity of ulna maximum measurement not at right angles to axis of forearm S C
19 Wrist depth contact measurement dorsal ventral at right angles to above S C (ordinarily)
20 Hand length third wrist crease to tip of index finger S C
21 Hand breadth at right angles to long axis of hand maximum base of digit II (index finger) to triquetral bone S C
22 Biocular (by palpation) right orbital border to left orbital border at *level of fronto zygomatic suture Sp C*
23 Bizygomatic maximum diameter across zygomatic crests Sp C
24 *Bigonial maximum diameter at gonial angles Sp C
25 *Head breadth maximum biparietal Sp C
26 *Head length from nasion to inion Sp C

INDICES

1 Ponderal index $\frac{\text{height } (\textit{in inches})}{\text{cube root of weight } (\textit{in pounds})}$ A measure of body mass such that the most massive physiques approach 10 0 and the most linear physiques approach 14 0 The massive physiques are relatively heavier per foot of stature

2 Thoracic index $\frac{\text{lower chest depth}}{\text{chest breadth}}$ x 100 A measure of chest roundness, such that the roundest chests approach 100

3 Relative span $\frac{\text{span}}{\text{height}}$ x 100 A measure of relative body length

4 Hip shoulder index $\frac{\text{hip breadth}}{\text{shoulder breadth}}$ x 100 A measure of relative hip breadth such that indices of 85 or over indicate broad hips i e feminoid proportions

5 Waist hip index $\frac{\text{waist breadth}}{\text{hip breadth}}$ x 100 A measure of the hip breadth such that indices under 80 indicate relatively narrow waists and somewhat feminoid appearance

6 Upper facial index $\frac{\text{upper face length}}{\text{bizygomatic distance}}$ x 100 A measure of relative face breadth such that a broader upper face results in a lower index

7 Eye face index $\frac{\text{bipupillary distance}}{\text{upper face length}}$ x 100 A measure of the relative eye face breadth such that a narrower interpupillary diameter results in a lower index

8 Nasal index $\frac{\text{nose breadth}}{\text{nose length}}$ x 100 A measure of relative nasal breadth

9 Shoulder index $\frac{\text{shoulder breadth}}{\text{height}}$ x 100 A measure of breadth of shoulders and therefore the reciprocal of linearity

10 Hand breadth index $\frac{\text{hand breadth}}{\text{hand length}}$ x 100 A measure of linearity of hands

11 Wrist breadth index $\frac{\text{wrist depth}}{\text{wrist breadth}}$ x 100 A measure of wrist roundness

12 Cephalic index $\frac{\text{head breadth}}{\text{head length}} \times 100$ A measure of roundness of head most used in racial comparisons

Comparison of coronary and control groups

MEASUREMENTS The ages of the two groups compared very closely the average age of the coronary heart disease group being 38 2 years and that of the unmatched control group 36 7 years The difference of + 1 5 years in favor of the coronary group is small and does not attain statistical significance Moreover changes due to age at this age level (35 to 40) are extremely small As described in Chapter I the two groups were quite comparable in socio economic status Their differences lay in factors considered to pertain especially to coronary heart disease

In addition to age and usual weight 24 measurements were made on both the coronary heart disease group and the unmatched control group One of these the biocular was not used in the analyses that follow Of the remaining 23 measurements 10 showed significant difference between the two groups—that is critical ratios (of the difference between the means) exceeding 2 5—while 3 others showed borderline significance—critical ratios equalling 2 0–2 5

The 14 measurements in Table 1 in which the control group exceeded the coronary heart disease group reflect in general the trend of the control group to be taller and more linear than the coronary heart disease group This difference is best seen in height (a difference of 4 5 cm) span total face length hand length and chest length Thus 7 of the 14 measurements in which the control group exceeded are length measurements

In 9 measurements out of 23 (age usual weight and biocular omitted) the coronary exceeded the control group although the control group was taller and longer It is of real importance to note that 8 of these 9 measurements relate to breadth the one exception being nose length which shows a difference that is not significant The two most significant depth measurements were those of the upper chest and wrist Thus despite the tendency of the coronary heart disease group to be shorter it was at the same time absolutely broader Therefore indices relating breadth to length would in general show the relatively greater breadth of the coronary heart disease group For the purposes of this study it has been our policy to keep such indices at a minimum

TABLE IV–1 Anthropometric measurements of coronary heart disease group of 97 males and unmatched control group of 146 males

	Coronary group mean ± S E	*Control group mean ± S.E*
Age (years)	38 2 ± 5	36 7 ± 6
Weight (lbs)	170 5 ± 2 3	177 0 ± 2 0*
Length measurements		
stature (cm)	171 8 ± 6	176 3 ± 7†
span (cm)	176 5 ± 8	179 6 ± 6*
chest length (cm)	21 5 + 2	22 4 ± 2†
nose length (mm)	56 7 + 4	56 2 ± 3
upper face (mm)	68 4 ± 5	69 6 ± 4
total face (mm)	121 1 ± 6	123 6 ± 6†
hand length (mm)	191 2 ± 9	193 8 ± 6*
head length (mm)	193 8 ± 8	195 7 ± 6
Breadth measurements		
shoulder breadth (cm)	39 2 ± 2	40 1 ± 2†
chest breadth (cm)	30 0 ± 2	30 2 ± 2
upper chest depth (cm)	19 5 ± 2	18 5 ± 2†
lower chest depth (cm)	23 0 ± 2	22 5 ± 2
hip breadth (cm)	29 5 ± 2	29 7 ± 1
waist breadth (cm)	29 5 ± 2	29 4 ± 2
hand breadth (mm)	88 8 ± 5	88 0 ± 4
wrist breadth (mm)	58 9 ± 4	58 6 ± 3
wrist depth (mm)	41 1 ± 3	39 9 ± 2†
bipupillary (mm)	62 8 ± 3	65 4 ± 3†
nose breadth (mm)	36 7 ± 3	36 1 ± 2
bizygomatic (mm)	141 1 ± 6	141 0 ± 4
bigonial (mm)	107 3 ± 5	108 2 ± 4
head breadth (mm)	153 8 ± 6	154 6 ± 5

*Differenc significant
†Difference highly significant.

The two groups were also compared with respect to their homo geneity for these anthropometric measurements that is their stand ard deviations were compared No important differences were noted except that the control group was more variable with respect to height However when height was compared with weight (ponderal index), there was no difference in absolute variability

INDICES Twelve indices were regularly employed in comparing the two groups In general they were chosen as having special utility in physique comparisons Two of the 12 however (nasal and ceph alic indices) were selected as having the least to do with physique and relating rather to racial differences

The indices in Table 2 were derived by analyzing statistically the original indices computed for each individual (that is they were based on primary measurements not on group averages)

TABLE IV–2 Anthropometric indices in coronary heart disease group of 97 males and unmatched control group of 146 males

Index	Coronary group mean ± S.E	Control group mean ± S E
Ponderal	12 25 ± 06	12 43 ± 05
Thoracic	76 8 ± 6	74 4 ± 5†
Relative span	102 9 ± 4	101 8 ± 2
Hip shoulder	75 5 ± 5	74 3 ± 4
Waist hip	99 9 ± 7	98 3 ± 4‡
Upper facial	48 7 ± 4	49 5 ± 5
Eye face	92 2 ± 7	94 1 ± 6
Nasal	65 1 ± 7	65 0 ± 5
Shoulder	22 9 ± 1	22 8 ± 1
Hand breadth	46 3 ± 5	45 3 ± 3‡
Wrist breadth	69 6 ± 1 0	68 2 ± 7
Cephalic	79 3 ± 6	79 0 ± 5

Difference significant. ‡Borderline significance
†Difference highly significant.

Table 2 indicates that the coronary heart disease group showed a uniform trend toward relatively greater depth and breadth Of the 12 indices there were 4 with significant differences and 2 others with borderline significance The coronary heart disease group was higher than the control group in 4 of these 6 indices and in 1 other index (ponderal) showed greater breadth by a decreased index In only 1 index (eye face) did the control group appear to have the significantly higher value If statistical significance is disregarded 10 out of 12 indices showed a tendency to greater breadth on the part of the coronary heart disease group

Two of the significant indices are the ponderal and the thoracic Their differences well illustrate the evidence that the coronary heart disease group was relatively heavier per foot of stature and that it showed central distribution of weight The distribution of the two groups according to ponderal index is given in Table 3

The relative hand breadth and the relative span also showed important differences The difference in relative hand breadth confirms the observational impression of lower linearity in the coronary heart disease group The control group had relatively longer narrower hands

The waist hip index shows that the coronary heart disease group despite its greater mass was not marked by a significantly broader waist

In contrast to the significant differences discussed above the

TABLE IV–3 Distribution of ponderal indices in coronary heart disease group of 97 males and unmatched control group of 146 males

Ponderal index	Coronary Group No	Coronary Group %	Control Group No	Control Group %
10 5–10 9	0	0 0	1	0 7
11 0–11 4	4	4 1	4	2 7
11 5–11 9	24	24 8	29	19 8
12 0–12 4	39	40 3	46	31 5
12 5–12 9	20	20 7	47	32 2
13 0–13 4	8	8 2	13	8 9
13 5–13 9	2	2 0	4	2 7
14 0–14 4	0	0 0	2	1 4

cephalic and nasal indices do not show significant differences These indices are in general of utility in racial analysis rather than in physique analysis and help to confirm the evidence that the two groups were relatively similar except in the respects noted

Indices are especially indicative of trends, for not being absolute measurements they eliminate differences in absolute size between the two groups Thus the difference in proportion continues to be evident both centrally and peripherally

EVALUATION OF WEIGHT Because of the attention now given to the term overweight and the concept of obesity especially as they might affect the etiology and prognosis of myocardial infarction it is well to review these terms before evaluating the weight factors in the present study

Overweight is at best a statistical concept referring to gross weight in excess of some standard selected for comparison

Obesity is on the other hand a morphological concept referring to softness corpulence and fatty deposits (obese excessively corpulent very fat —*Webster s New International Dictionary*) Although it is possible to set objective standards of obesity so that individual judgments can be validated as by the use of the McCloy fat calipers (McCloy 1936) ordinarily no such standards are set and the interpretation is dependent to a large degree upon the personal bias of the investigator which is in turn a function of his experience and clientele Despite this objection to the term the concept of obesity has real pertinence in clinical study for one can view directly the encompassing fatty deposits and decide whether the subject is carrying more fat than is useful This firsthand evaluation is far superior to any table of norms

The difficulty of rating obesity and the even greater difficulty of trying to make the rating on the cadaver or from hospital records rather than directly have led to the practice of making determina tions of overweight as a measure of obesity Overweight ratings may customarily mean (*a*) any value above an arbitrary norm (*b*) some fixed value above a norm or (*c*) some fixed percentage above a norm Furthermore overweight must be considered in terms of the individual and it is obvious that the simple word overweight does not describe physique

McCloy states the same problem *

This normal weight must be interpreted in terms of the individual s build The slender linear type of individual is and should be lighter in weight for the same height than the stocky lateral type of individual For purposes of predicting what this normal weight should be some standards must be devised These will be primarily measurements involv ing the *size of the skeleton both as to dimensions of the thoracic cage* and hips and as to the thickness or coarseness of the long bones Only when the standard weight has been computed from such fundamental bases can under and overweight be considered significant enough to be used in directing the hygienic regimen

The second measurement of nutritional status is the relative amount of fat. The amount of fat underlying the skin needs to be measured and a norm or standard found to determine whether or not the fatty deposits of any given individual are greater or less than the optimum amount Fat also enters into the problem of under- and overweight but it is partly a factor to be measured and interpreted separately

The third measurement used in nutritional status studies is that of the normal development of muscle This will be considered under two general headings (1) muscle as it makes up the general nutritional background of the body and (2) muscle as an organ for strength It is well established that muscular development is one of the factors deter mining adequate weight for any given type and the lack of this muscular *development is frequently* associated with chronic poor nutrition

Sheldon writes on the problem of differential weight norms †

We do a great unkindness to those trusting people who still believe in the divinity of the printed word when we allow the usual publications

*C H McCloy *Appraising Physical Status The Selection of Measurements* University of Iowa Studies in Child Welfare 1936 pp 33–34 Quoted by permis sion of the publishers

†W H Sheldon S S Stevens and W B Tucker *The Varieties of Human Physique* Harper & Bros New York 1940 p 2 6 Quoted by permission of the publishers

sitated a physique rating system marked by the following features

1 It would follow the concept of morphological constitution—"the principle that the individual's bodily habitus is unchangeable once it is established (Williams, 1933), distinguishing between habitus and nurture
2 It would be age corrected so that age and nutritional features would not be confused with constitutional differences, nor would one age be used as a standard for all ages
3 The individual would be rated numerically and without reference to types"
4 The ratings would show useful correlations'

Somatotype method

While the vast majority of physique rating systems (Kretschmer's Viola's and others) have employed bipolar or even tripolar typologies thus necessitating a few extreme or pure types and a large mixed category the Sheldonian system of somatotyping makes use of three polar extremes only as directions and designates the various combinations in terms of distance along the three directions

To quote Sheldon (1940) Physique is a continuum and any system of rating must have as its purpose the location of the individual on the three dimensional spectrum of physique" The numerical rating system in the Sheldonian method performs that function Thus the rating in the Sheldonian sense avoids typology though the terminology makes it possible to designate the position of the physique in words as well as in numbers

In this system each individual is given a rating expressed in three numbers, each representing the *relative dominance* of one physique component or direction The highest number represents the dominant component the next highest number the secondary component, and the lowest the least prominent component The three number rating thus immediately assigns the individual to his position on a tri coordinate physique spectrum (Sheldon 1940 1942 1949 Hooton 1945, 1946 Seltzer 1943 1946 1948 Seltzer and Brouha 1943 Bullen and Hardy 1946)

According to the conventions of the system the minimum number for each component is set at 1 (that is each component must be represented to some degree) and the maximum is set at 7 Thus

The difficulty of rating obesity and the even greater difficulty of trying to make the rating on the cadaver or from hospital records rather than directly have led to the practice of making determinations of overweight as a measure of obesity Overweight ratings may customarily mean (*a*) any value above an arbitrary norm (*b*) some fixed value above a norm or (*c*) some fixed percentage above a norm Furthermore overweight must be considered in terms of the individual and it is obvious that the simple word overweight does not describe physique

McCloy states the same problem *

This normal weight must be interpreted in terms of the individual s build The slender linear type of individual is and should be lighter in weight for the same height than the stocky lateral type of individual For purposes of predicting what this normal weight should be some standards must be devised These will be primarily measurements involving the size of the skeleton both as to dimensions of the thoracic cage and hips and as to the thickness or coarseness of the long bones Only when the standard weight has been computed from such fundamental bases can under and overweight be considered significant enough to be used in directing the hygienic regimen

The second measurement of nutritional status is the relative amount of fat The amount of fat underlying the skin needs to be measured and a norm or standard found to determine whether or not the fatty deposits of any given individual are greater or less than the optimum amount Fat also enters into the problem of under and overweight but it is partly a factor to be measured and interpreted separately

The third measurement used in nutritional status studies is that of the normal development of muscle This will be considered under two general headings (1) muscle as it makes up the general nutritional background of the body and (2) muscle as an organ for strength It is well established that muscular development is one of the factors determining adequate weight for any given type and the lack of this muscular development is frequently associated with chronic poor nutrition.

Sheldon writes on the problem of differential weight norms †

We do a great unkindness to those trusting people who still believe in the divinity of the printed word when we allow the usual publications

*C H McCloy *Appraising Physical Status The Selection of Measurements* University of Iowa Studies in Child Welfare 1936 pp 33–34 Quoted by permission of the publishers

†W H Sheldon S S Stevens and W B Tucker *The Varieties of Human Physique* Harper & Bros New York, 1940 p 226 Quoted by permission of the publishers

of height weight age norms to go unexplained It is sorrowful to hear the lament of a [woman] who is already 30 pounds overweight, but who reads daily on the printed scales that she is 30 pounds underweight And the poor [man] who weighs 99 pounds reads with horror that he should weigh 178 This kind of foolishness gives some of our best people inferiority complexes and then they have to be analyzed or sent to church

In order to study the problem of overweight' we have followed the method of Levy et al (1946) and have computed the deviation between a norm (for height and age for each person) and the actual weight This has been accomplished for the coronary heart disease group and for the unmatched group of 146 controls as well

The comparison between the coronary heart disease patients and the unmatched controls was also made in terms of five year age groups—21–25, and so on—with reference to the appropriate norms Both the coronary heart disease patients and the controls showed excessive weight with reference to the Army norm The amount of excessive weight varied from age group to age group being largest in the 26 to 30 year category However the pattern of excess weight by age group was essentially the same in the coronary heart disease group and in the unmatched control group The average deviations from the Army norms were + 19 1 ± 1 9 pounds and + 18 5 ± 2 1 pounds respectively (Garn Gertler Levine and White 1951)

Such criteria must be based on factors of age sex body build and height The Army standards of age height and weight partially fulfill these requirements and the resulting weight norms can serve as a baseline with which any group or groups may be compared If two groups have been thus compared with the base line it is then valid to compare them with each other This was done in the present study with the result that both the coronary and the unmatched control groups showed approximately the same degree of overweight with respect to the Army norms Since the unmatched controls represented a good cross section of the American population the logical implication is that the whole American male population is overweight The unsatisfactory nature of norms that suggest the deviation of an entire population from normal is evident However until more adequate criteria are developed these norms serve as a valid baseline for comparison of data

Rating of Physique

As indicated previously a major problem for consideration in this study is neither weight nor overweight nor even obesity itself but rather a comparison of the physical characteristics of two groups to determine whether the differences or similarities in weight and in weight indices may be due to different proportions of constituent tissues In other words the problem is physique rating There are three possible methods of rating (1) dividing the individuals into discrete typological entities or types (2) dividing some single continuum such as that of height/cube root of weight into equal intervals or (3) employing a new system forming a continuum

The first or typological classification is based on physique ap praisal with or without the supplementary aid of anthropometric measurements or indices Kretschmer s typologies (1925 1945) are perhaps the best known example In the system of this Bavarian clinician there are the following types (*a*) pyknic (*b*) athletic (*c*) asthenic and (*d*) mixed The pyknics are robust and florid the asthenics are linear the athletics are well muscled but linear and the mixed category is what it implies Thus the system widely used in medical studies presents individuals in terms of discrete categories Its major disadvantage is that the mixed group usually includes most individuals and the system makes no allowances for age changes that is with advancing years and corpulence more individuals end up in the first category at the expense of the athletic asthenic and mixed categories Williams writing in Cowdry s *Arteriosclerosis* (1933) asks pertinently whether some observers have confused the appearance of good nurture and obesity with that of the sthenic habitus

McCloy (1936) and his associates have analyzed Kretschmer s system (1925 1945) by means of indices especially the height/cube root of weight index They find no evidence of bimodality (which would be true if there were two populations one of laterals and one of linears) However although McCloy and his co workers favor a constitutional appraisal based on the height/cube root of weight index they also hold to the idea of linear and lateral types with this addition—that due attention and correction should be made for fat and muscle Willoughby *(1932) has devised ideal* weight standards similarly based on structure for the adult

It was apparent then that the requirements of this study neces

sitated a physique rating system marked by the following features

1 It would follow the concept of morphological constitution— the principle that the individual s bodily habitus is unchangeable once it is established (Williams 1933) distinguishing between habitus and nurture
2 It would be age corrected so that age and nutritional features would not be confused with constitutional differences nor would one age be used as a standard for all ages
3 The individual would be rated numerically and without reference to types
4 The ratings would show useful correlations '

Somatotype method

While the vast majority of physique rating systems (Kretschmer s Viola s and others) have employed bipolar or even tripolar typologies thus necessitating a few extreme or pure types and a large 'mixed category the Sheldonian system of somatotyping makes use of three polar extremes only as directions and designates the various combinations in terms of distance along the three directions

To quote Sheldon (1940) Physique is a continuum and any system of rating must have as its purpose the location of the individual on the three dimensional spectrum of physique The numerical rating system in the Sheldonian method performs that function Thus the rating in the Sheldonian sense avoids typology, though the terminology makes it possible to designate the position of the physique in words as well as in numbers

In this system, each individual is given a rating expressed in three numbers each representing the *relative dominance* of one physique component or direction The highest number represents the dominant component the next highest number the secondary component, and the lowest the least prominent component The three number rating thus immediately assigns the individual to his position on a tri coordinate physique spectrum (Sheldon 1940 1942 1949 Hooton 1945 1946 Seltzer 1943 1946 1948 Seltzer and Brouha 1943 Bullen and Hardy 1946)

According to the conventions of the system the minimum number for each component is set at 1 (that is each component must be represented to some degree) and the maximum is set at 7 Thus

each of the three numbers in the system may theoretically vary between 1 and 7 However the components necessarily show inter correlations such that a change in any one component usually shows a corresponding but not necessarily equal change in one of the other two (for example if one man is more muscular than another he is likely to be less linear) The order of components in the three digit numbers is always the same endomorphy mesomorphy ectomorphy (these may be referred to as the first second and third components respectively)

The names of the three components are selected to recall the primary germ layers that are in part represented in them though it should be stressed that the names are largely mnemonic devices and should not be taken to imply that a component refers entirely to a particular germinal layer (Hunt 1949)

Endomorphy is the component of softness roundness and smoothness but not necessarily fat An endomorph may be a rounded smoothed-off individual without being frankly obese though the extreme endomorph usually becomes obese Diagnostic features include blunt chin neck angle deep round thorax pneumatic appearance hamming of upper arms juxtaposition of thighs and (usually) genu valgum small features and anteroposterior diameters greater than transverse

Mesomorphy is the component of muscularity bone mass angularity of outline and contour A mesomorph has large bones and joints (and is thus recognized even in age) a sharp chin neck angle a deep thorax good shoulder muscles usually a triangular shoulder to hip tapering in both sexes heavy leg muscles and broad hands Even combined with considerable endomorphy the mesomorph is still easily distinguishable

Ectomorphy is the component of linearity fragility elongation The ectomorph has long fingers long toes long narrow hands and feet a long frequently shallow thorax long femora often a pinched waist The extreme ectomorph is distinguished from the merely emaciated individual by these structural criteria

Rating is accomplished from the standardized carefully posed photograph together with height weight data (using a table for certain age levels) data on the patient s health history and preferably a view of the subject himself Research somatotyping has as its purpose the rating of the individual s potential in physique

and should not be attempted without available medical data This is especially important in the study of a disease group (such as the present) where the patients are of varying ages and where it is necessary to determine whether these patients have physique factors in common

After viewing the standardized photographs and the other data the *dominant* component is first determined by inspection or (when difficult) after referral to previously rated photographs Then the *secondary dominance* is determined Finally the numerical ratings are applied Usually when the dominance is recognized, its degree is immediately apparent This is not always the case however the subject may be a 7 (extreme) in endomorphy, but the secondary (mesomorphic) component may require further study to determine whether it is a 3 or a 2

It will be seen that this method of rating differs from others used previously by noting not only the direction (dominance) but also the distance along that direction to which the physique extends A 7–1–1 and a 4–3–3 are both dominant endomorphs but the difference is major Not always is one component clearly dominant in some cases two components may be about equal, as in the 5–5–1 the 4–4–2 and others In still other and rarer cases all three components are about equal or balanced such is the 4–4–4 a mean but by no means modal physique Typical ratings are

Dominant endomorphs 7–1–1 7–2–1 7–3–1 6–2–2 6–3–1, 5–4–1

Dominant mesomorphs 1–7–1 2–6–2 3–5–3 4–5–1, 2–5–4

Dominant ectomorphs 2–2–6 1–1–7 1–2–7 2–3–5, 2–4–5

Mid ranges 4–4–4 4–4–3 4–3–3 3–3–4 3–4–4

While the numbers immediately fix the position of the individual on the tri coordinate somatotype triangle and it is possible to visualize the approximate location of any physique against this triangle for convenience in speaking and writing it has been agreed to employ the principal dominance as a noun and the secondary modifying dominance as an adjective Hence in the latter part of this chapter we will call a person who has a 4–6–1 physique an *endomorphic mesomorph* (meaning a mesomorph with endo morphic modification) one who has a 6–4–1 physique a *meso morphic endomorph* and so on

Certain physiques are easy to rate at any age these include the extremes—1–1–7 7–1–1 1–7–1—as well as the other polar physiques Other physiques are much more difficult for the inexperienced to rate at older age levels This is especially true of the endomorphic mesomorphs and mesomorphic endomorphs Both are quite round in the late forties But when one is compared with the other the difference becomes quite apparent it is a function of the strength of the second (mesomorphic) component The mesomorphic endomorph like the dominant endomorph is round pneumatic and we find often a difficult subject for venipuncture But the endomorphic mesomorph though paunchy is high paunched frequently still rugged in outline We include examples of the differences between these physique groupings * (See below under Classification by Dominances or Types for other examples of the coronary heart disease physiques)

*The physiques 7–2–1 7–3–1 6–3–3 and the like are fre*quently difficult to distinguish in later age groups because they are all fat and the supporting mesomorphy is difficult to assess However in our coronary heart disease group such mesopenic endomorphs are rare

Method used in present study

In the course of this study it has been possible to employ not only the information provided by the immediate appearance of the individual but also all the valuable data provided by the interview the health history and the information provided on occupation and athletic interests Naturally far more data were obtained on the young coronary heart disease patients (who were subjected to an intensive interview) than on the controls However in the unmatched control group records were made of the weight at 21–25 years of age maximum weight occupation and athletic interests therefore the final ratings were based on a more detailed knowledge of the individual than his momentary appearance alone would have provided

PROCEDURE FOR EXAMINATION With the available information the rating was made in the following manner

*On the other hand it has been shown by Lasker (1947) that the accurate somatotyping of starvation cases is difficult Luckily only one of the cases in the present group comes under this heading

1 The weight and height were taken
2 Anthropometric measurements were made
3 The patient s weight and health history were considered
4 Ratings of body configuration were made
5 The somatotype photograph was taken
6 The patient was kept on the somatotype stand the spot points were noted and, after palpation of the patient an impression somatotype was made usually after a concurrence by the two observers
7 After the printed photograph was returned, the impression somatotype was corrected, if necessary This rarely required shifting of component dominance and usually consisted of adjustment between two closely related somatotypes e g 3–5–2 and 4–5–2

In the course of this work we learned that some of the inspectional criteria used by Sheldon (1940) were applicable to all age levels Most conspicuous of these were

1 Trapezius development
2 Chin neck angle
3 Development of clavicles
4 Biceps and triceps form with the arms in the somatotype position
5 Triangular form of the torso (dorsal view)
6 Relative shoulder hip size
7 Sacral angle (back curve)
8 Relative torso–leg length

On the other hand criteria that applied to softness of outline (endomorphy) were less applicable in our groups (which were about twenty years older than his) except for the somatotype low in endomorphy

It has been our experience with the impression somatotype that fairly good ratings of the second (mesomorphic) component are possible since the general configurations—muscularity of legs arms shoulders and back—are all visible and palpable but that the first (endomorphic) component is apt to be underestimated especially in the older male Since a number of the referring physicians were interested in our rating system we were curious to see how their appraisals correlated with our own The only marked discrepancy appeared with ectomorphic mesomorphs who were considered by them to be ectomorphs probably because they were more familiar with the typology of Kretschmer (1945)

TABLE IV–4 Dominant physiques in coronary heart disease group of 97 males and unmatched control group of 146 males

	Coronary group ♂	*Control group* ♂
Endomorphs	25 7	29 9
Mesomorphs	42 2	19 8
Ectomorphs	7 3	21 1
Mid range	17 5	18 4
Two balanced	7 3	10 8

CLASSIFICATION BY DOMINANCES OR TYPES As a first rough sorting the individual ratings were divided into

1 Dominant endomorphs—6–2–2 6–4–1 5–3–3 and so forth
2 Dominant mesomorphs—2–5–3 4–5–1 2–6–2 and so forth
3 Dominant ectomorphs—2–4–5 2–3–5 2–2–6 and so forth
4 Mid range physiques—4–4–4 3–4–4 4–4–3 and so forth
5 Two balanced somatotypes—5–5–1 2–4–4 and so forth

This preliminary sorting was done to see if there was evidence that major differences existed in one component It was especially important to see whether the coronary heart disease group showed more endomorphs in view of the data presented earlier in this chapter

As shown in Table 4 there was evidence that the coronary heart disease group and the control group differed in the distribution of their dominant components The major differences (see Figures 1 and 2) occurred within the category of dominant endomorphy the differences between the percentages showing secondary meso morphic and ectomorphic components were statistically significant The percentages falling into the category of endomorphy as a whole however showed no significant difference

It was noted that the ectomorphs in the coronary heart disease series were entirely mesomorphic ectomorphs that is well muscled linear men

To summarize in comparison with the control group the coronary heart disease group showed

1 About the same proportion of dominant endomorphs
2 About twice as many dominant mesomorphs
3 Less than half as many dominant ectomorphs
4 About the same proportion of mid range physiques
5 About the same proportion of two balanced physiques

PERCENTAGE OF ALL PATIENTS
50
40
30
20
10
0
Balanced Mesomorphs
Ectomorphic Mesomorphs
Balanced Endomorphs
Mesomorphic Endomorphs
Mesomorphic Ectomorphs
Endo-Meso
Meso-Ecto
ENDOMORPHS
MESOMORPHS
ECTOMORPHS
MID RANGE
BALANCED SOMATOTYPES
DOMINANCES EVIDENT
DOMINANCES NOT EVIDENT

FIGURE IV–1 Distribution of physiques among 97 *young male coronary heart disease patients* In this group the mesomorphs were the most common while ectomorphs were surprisingly rare

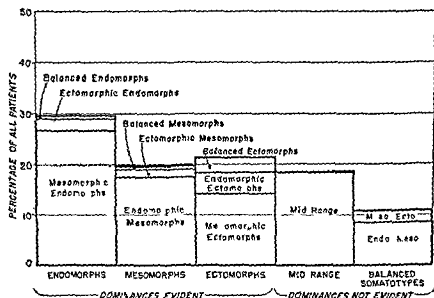


FIGURE IV–2 Distribution of physiques among 146 unmatched controls In this group the endomorphs had a slight predominance

FIGURES 3–9 SHOW THE VARIETY OF SOMATOTYPE RATINGS FOUND IN THE CORONARY HEART DISEASE GROUP

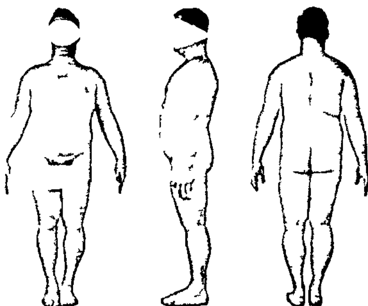


FIGURE IV 3 Somatotype endomorphy 5 1 2 mesomorphy 6 ectomorphy 1 Age 29 h [illegible] ght 5 8 1/[illegible] weight [illegible]37 lbs

PERCENTAGE OF ALL PATIENTS

Balanced Mesomorphs

Ec omorphic M somo phs

End morph Mesomorphs

Balanced Endomorphs

Mesomo ph c Endomo phs

Mesomor h c Ectomorphs

Endo-Meso

M so-Ecto

ENDOMORPHS MESOMORPHS ECTOMORPHS MID RANGE BALANCED SOMATOTYPES

DOMINANCES EVIDENT — DOMINANCES NOT EVIDENT

FIGURE IV-1 Distribution of physiques among 97 young male coronary heart dis ease patients In this group the mesomorphs were the most common while ectomorphs were surprisingly rare

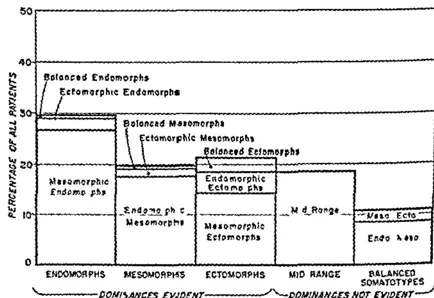


FIGURE IV-2 Distribution of physiques among 146 unmatched controls In this group the endomorphs had a slight predominance

FIGURES 3–9 SHOW THE VARIETY OF SOMATOTYPE RATINGS FOUND IN THE CORONARY HEART DISEASE GROUP

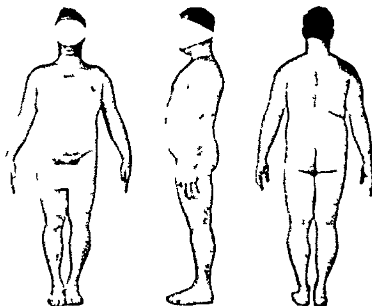


FIGURE IV–3 Somatotype endomorphy 5 1 . mesomorphy 6 ectomorphy 1 Age 29 h ight 5 8 1 2 weight .37 lbs

50
40
30
20
10
0
PERCENTAGE OF ALL PATIENTS
Balanced Mesomorphs
Ectomorphic Mesomorphs
Endomorphic Mesomorphs
Balanced Ectomorphs
Mesomorphic Endomorphs
Mesomorphic Ectomorphs
Endo-Meso
Meso Ecto
ENDOMORPHS
MESOMORPHS
ECTOMORPHS
MID RANGE
BALANCED SOMATOTYPES
DOMINANCES EVIDENT
DOMINANCES NOT EVIDENT

FIGURE IV–1 Distribution of physiques among 97 young male coronary heart disease patients In this group the mesomorphs were the most common while ectomorphs were surprisingly rare

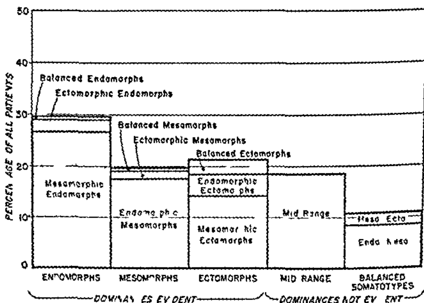


FIGURE IV–2 Distribution of physiques among 146 unmatched controls In this group the endomorphs had a slight predominance

FIGURES 3–9 SHOW THE VARIETY OF SOMATOTYPE RATINGS FOUND IN THE CORONARY HEART DISEASE GROUP

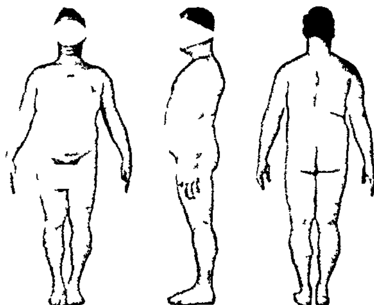


FIGURE [illegible] 3 Somatotype endomorphy 5 1 [illegible] mesomorphy 6 ectomorphy 1 Ag[illegible] 9 [illegible] [illegible]ht 5 8 1 [illegible] weight [illegible]37 lbs

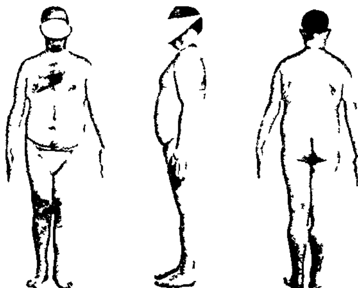


FIGURE IV–4 Somatotype endomorphy 5 mesomorphy 4 1 2 ectomorphy 1 Age 37 height 5 2 weight 152 lbs

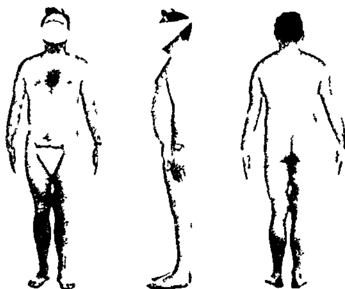


FIGURE IV–5 Somatotype endomorphy 5 mesomorphy 4 1/2 ectomorphy 1 Age 38 height 5 3 weight 16_ lbs

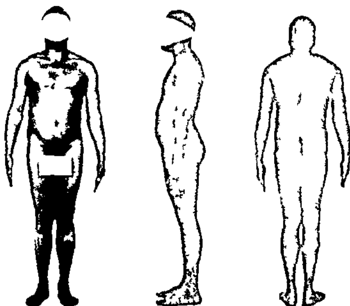


FIGURE IV–6 *Somatotype endomorphy 2 1 mesomorphy 5 1 ectomorphy 2 1/– Age 39 height 5 7 1 2 weight 180 lbs*

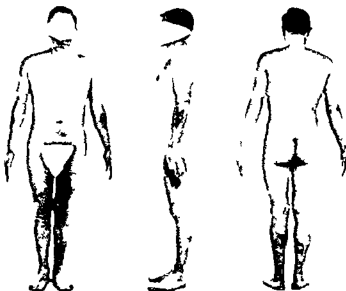


FIGURE 1 Somatotype endomorphy 3 mesomorphy 6 ectomorphy 1 Age 41 height 6 weight 175 lbs

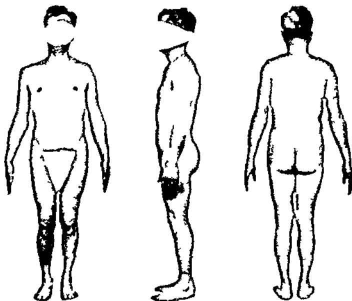


FIGURE IV–8 Somatotype endomorphy 3 mesomorphy 4 ectomorphy 3 Age 36 height 5 5 weight 162 lbs

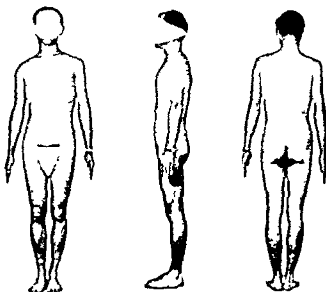


FIGURE IV–9 Somatotype endomorphy 2 mesomorphy 3 ectomorphy 5 Age 25 height 5 5" weight 130 lbs

Figures 3 through 9 illustrate the variety and range of component ratings observed *in the coronary heart disease group*

It is of some interest to note also the physique of the 3 female patients who are not included in the rest of this discussion Two women were dominant mesomorphs whose secondary dominance *was endomorphy The third* was a dominant ectomorph with secondary mesomorphy

DISTRIBUTION OF CORONARY GROUP As mentioned before physique is represented as a three dimensional continuum in the somatotype system The method of dividing the somatotypes into dominant endomorphs mesomorphs ectomorphs and mid range physiques may therefore be misleading for it forces more rigid categorization than is absolutely necessary To the advanced worker such a fourfold division smacks too strongly of the familiar rigid types and the defects of the Kretschmerian system In our present study we can also see that the arbitrary separation of endomorphic mesomorphs from mesomorphic endomorphs creates a dichotomy not found in nature Thus the preceding section though illustrative of the relative frequency of certain physiques in the continuum requires more careful interpretation

An alternative method devised by Sheldon which is probably superior to the fourfold division is that of plotting the distribution of cases directly on the somatotype triangle Here adjacent points are related somatotypes whether the dominances are the same or *not* As we *mentioned earlier the components are directions and* the equal interval increments are distances along these directions Thus for a two dimensional surface the three components can be represented as three equal length vectors and the resultant figure is shown to be a triangle (*Sheldon 1940 p 118*) *On this* figure any somatotype can be plotted according to its vector position and then read

When we plot the 97 young male patients in the coronary group we note a clumping in the upper left sector of the triangle an absence of peripheral positions and a concentration in the *mesomorphic sector We see that the distribution* of coronary *heart* disease cases clumps in the massive muscular northwest corner

In contrast our control group of 146 males shows a more general distribution a wider spread and a more equitable division (though with some degree of skewing)

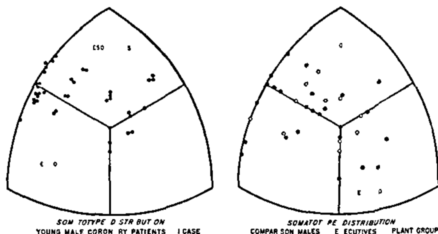


FIGURE IV–10 Somatotype distributions of coronary heart disease group of 97 males and unmatched control group of 146 males The patients showed a marked deficiency in ectomorphy and a deficiency in endomorphy The physique dis tribution in their group was more compact

The distribution in the lower region of the somatotype triangle is especially noteworthy while the endomorphs and ectomorphs with low mesomorphy are well represented in the control group the comparable area is blank for the coronary heart disease group (Figure 10)

Summary

There has long been speculation concerning the relation be tween body build body weight and longevity The trends of thought on this topic have always been concerned with an association be tween (*a*) longevity and leanness and (*b*) cardiovascular disease and obesity The definitions of overweight leanness and obesity have not been entirely satisfactory Accordingly this study attempted to delineate overweight and body build in a more definitive manner Body weight in the coronary heart disease group and in the control group was compared with a weight norm for age and height computed from Army standards From this comparison it was demonstrated that the coronary heart disease group was not overweight in relation to the control group By employing the Sheldon system of physique classification it was learned that coro nary heart disease is significantly associated with a specific body

habitus rather than with body weight These body types were further delineated by careful anthropometric measurements It was clearly demonstrated that the endomorphic mesomorph—the fat muscular person—is most prone to coronary heart disease while the ectomorph—the lean person—is the least prone to coronary heart disease

REFERENCES

Arteriosclerosis A Survey of the Problem ed by E V Cowdry Macmillan New York 1933

BAUER, J *Constitution and Disease* 2nd Ed Grune & Stratton New York 1945

BULLEN A K and HARDY H L Analysis of body build photographs of 175 college women *Am J Phys Anthropol* 4 37–68 1946

CIOCCO A The historical background of the modern study of constitution *Bull Inst Hist of Med* 4 23–38 1936

DRAPER G The mosaic of androgyny maleness within female and femaleness within male *New England J Med* 225 393–401 1941

DRAPER G DUPERTUIS C W and CAUGHY J L JR *Human Constitution in Clinical Medicine* P B Hoeber Inc New York 1944

DUBLIN L I and MARKS H H Mortality of women according to build—experience in substandard issues Proc A Life Insur M Dir America 22 1938

DUBLIN L I and MARKS H H The weight standard and mortality of very tall men *Proc A Life Insur Dir America* 23 153–181 1937

FRENCH A J and DOCK W Fatal coronary arteriosclerosis in young soldiers *J A M A* 124 1233–1237 1944

GARN S M GERTLER M M LEVINE S A and WHITE P D Body weight versus weight standards in coronary artery disease and a healthy group *Ann Int Med* 34 1416–1420 1951

GLENDY R E LEVINE S A and WHITE P D Coronary disease in youth comparison of 100 patients under 40 with 300 persons past 80 *J A M A* 109 1775–1781 1937

GOLDSMITH G A and WILLIUS F A Body build and heredity in coronary thrombosis *Ann Int Med* 10 1181–1186 1937

HOOTON E A *Young Man You Are Normal* G P Putnam s Sons New York 1945

HOOTON E A *Up from the Ape* Rev Ed Macmillan Co New York 1946

HUNT E E JR A note on growth somatotype and temperament *Am J Phys Anthropol* 7 79–89 1949

KOVACS J and HARTNUNG E F Constitution and arthritis *J Lab & Clin Med* 21 1022–1027 1935

KRETSCHMER E *Korperbau und Charakter* 1st Ed J Springer Berlin, 1921 Tr from 2nd German ed into English by W J H Sprott, *Physique and Character* Kegan Paul Trench Trubner London 1925 2nd rev ed 1945

LASKER G W The effects of partial starvation on somatotype *Am J Phys Anthropol* 5 323–341 1947

LESSA W A Appraisal of constitutional typologies Memoirs No 62, American Anthropological Assoc 1943 (Am Anthropologist, new ser vol 45 no 4)

Levine S A and Brown C L Coronary thrombosis its various clinical features *Medicine* 8 246–418 1929

Levy R L White P D Stroud W P and Hillman C C Overweight its prognostic significance *J A M A* 131 951–953 1946

Martin R *Lehrbuch der anthropologie* I 2nd Ed Springer Berlin 1928

McCain F H Kline E M and Gilson J S A clinical study of 281 autopsy reports on patients with myocardial infarction *Am Heart J* 39 263–272 1950

McCloy C H and others *Appraising Physical Status The Selection of Measurements* University of Iowa Studies in Child Welfare Iowa City 1936

Moritz A R and Zamcheck N Sudden and unexpected deaths of young soldiers *Arch Path* 42 459–494 1946

Newman M Coronary occlusion in young adults *Lancet* 2 409–411 1946

Pearl R An index of body build *Am J Phys Anthropol* 26 315–348 1940

Pearl, R and Ciocco A Studies on constitution II Somatological differences associated with di ease of the heart in white males *Human Biol* 6 650–713 1934

Petersen W F Constitution and disease *Physiol Rev* 12 283–308 1932

Seltzer C C Anthropometry and arthritis *Medicine* 22 163–203 1943

—— The relationship between the masculine component and personality *Am J Phys Anthropol* 3 33–47 1945

—— Anthropometric characteristics and physical fitness *Research Quart* 17 10–20 1946

—— A relationship between Sheldonian somatotype and psychotype *J Personality* 16 431–436 1948

Seltzer C C and Brouha L Masculine" component and physical fitness *Am J Phys Anthropol* 1 95–108 1943

Sheldon W H Hartl E M and McDermott E *Varieties of Delinquent Youth* Harper & Bros New York 1949

Sheldon W H and Stevens S S *The Varieties of Temperament* Harper & Bros New York 1942

Sheldon W H Stevens S S and Tucker W B *The Varieties of Human Physique* Harper & Bros New York, 1940

Viola G *La costituzione individuale* L Capelli Bologna 1933

White P D *Heart Disease* 3rd Ed Macmillan Co New York 1944

Williams G D in *Arteriosclerosis a survey of the problem* Ed by E V Cowdry Macmillan Co New York, 1933

Willoughby D P An anthropometric method of arriving at the optimal proportions in any adult individual *Research Quart* 3 48–77 1932

Yater W M Traum A H Brown W G Fitzgerald R P Geisler M A and Wilcox B B Coronary artery disease in men eighteen to thirty nine years of age *Am Heart J* 36 334–372 481–526 683–722 1948

CHAPTER V

Athletic Activity and Occupations

Athletic Activity

A NUMBER of previous investigators had reported that athletic histories were common among those who experienced coronary heart disease early in life (Levine and Brown 1929 White 1944 Newman 1946) In order to elaborate on these reports and to investigate athletic participation more thoroughly all the coronary patients in the study were questioned as to their previous athletic activities Because athletics is an integral part of the American scene and the majority of males have participated in some sport at some time in their lives, the interview was carefully conducted in order to separate casual players from regular participants in organized athletics

First each man was asked whether he had participated in athletics during grammar school If the reply was affirmative he was asked what sports had been involved and to what extent and whether the teams had been intramural or interscholastic The same questions were repeated for the period of secondary education The men were asked whether they had been on regular high school teams and whether they had won letters or similar awards Those *who had gone to college were queried in a similar manner* Lastly the question of professional or semiprofessional athletics was brought up

In the event of negative replies the interviewer attempted to discover whether the lack of participation was involuntary or voluntary Involuntary non participation was recorded when the subject s school had no athletic programs when he had to work on the farm or support the family or when non participation was forced by chronic disease It is noteworthy that two men who had not been allowed to participate in school athletic programs because of a history of rheumatic fever later participated extensively in club and local athletics

TABLE V–1 Athletic records of coronary heart disease group of 97 males

Athletic activity	*No of patients*	%
GRAMMAR SCHOOL		
Went to grammar school but not beyond	20	100
highly athletic* in grammar school	3	15
not athletic in grammar school but athletic in later life	5	25
HIGH SCHOOL		
Went to high school but not beyond	46	100
starred in major athletics†	23	50
starred in minor athletics	12	26
unable to participate had to work	8	17
unable to participate poor health	3	7
COLLEGE		
Went to college	31	100
starred in college major athletics†	5	16
unable to participate had to work	2	6

*Participated in all the organized sports the school allowed
†Baseball and football

The men in the coronary heart disease group were divided into three categories (*a*) those who did not go beyond grammar school (*b*) those who did not go beyond high school and (*c*) those who completed college Accordingly the athletic histories were completed for the highest educational level, that is if a man went through college he was not included in either the high school or grammar school group The results are tabulated in Table 1

In the high school category, 50 per cent starred in major athletics this proportion appears to be unusually high in contrast to the total percentage of boys who received one or more letters in football at the high schools attended by many of the coronary heart disease patients in Providence and Boston In these schools 10 05 per cent from a group of 1 091 received letters At Harvard University 6 per cent of the students received letters in major sports a somewhat lower proportion than the 16 per cent in the coronary heart disease group who received letters for major athletics while attending college

Six of the total group of 97 patients went on to semiprofessional or professional athletics Another was a skilled competitive skier Many others remained interested in athletics after their school days and participated in soccer volleyball and other club or Y M C A sports

There appears to be an association between the coronary condi

tion and the athletic participation It must not be concluded how ever, *that athletics and coronary heart disease are causally related* It is not to be said that participation in athletics is responsible for the myocardial infarction Rather the athletic histories of these individuals is a function of their mesomorphy and the large num ber of ex athletes in the series is related to the disproportionate number of mesomorphic individuals in the series In fact the most athletic individuals in the group did have the highest average meso morphy score 4 85

Thus it may be concluded that (*a*) among the patients in this series there appears to be an unusually large proportion with athletic histories as measured by regular participation and awards in the contact sports (baseball and football) as well as in less organized individual sports (skiing and so on) (*b*) the high degree of athletic participation is in accord with the predominance of mesomorphic individuals in the series and (*c*) coronary heart disease and athletic participation may well be related only through the common factor of mesomorphy

Occupations

Various views are held about the possible relationship of eco nomic position and occupation to the development of coronary ... ...rosis These range from the view of Brock Chisholm ... disease is ... reiterates the commonly held idea that diseases of the ... in manager... are disproportionately a disability of the rich to ... frequency of ... (1949) and Boas and Donner (1932) who have observed howe... ...rt disease to be surprisingly frequent among ... talents may aug... ...e fact that these groups were Jewish may in... tions who are a... since it is known that the disease is more include hereditar... population Unfortunately the many con... ances in lipid met... *complicated by the fact that the sorting* ... d that in some studies women are in... s they are not Moreover racial data ... occupational groupings are made in ... e...n of the kind of work involved ... te (1939) surveyed 3 400 unselected ... chusetts General Hospital and found ... clusion (but not of acute coronary ... in private patients as in ward patients ... versely if ... we assume th...

BOAS E P *Coronary Art*...
BOAS E P and DONNER ... 98 2186–2189 1932
CHISHOLM B Social medic...
GORDON W H BLAND E F ... ...m *Am Heart J* ... nd BROWN C ... 415–418 1929

Thus a selection made for the most part on a purely economic basis gave a highly significant indication Master et al (1939) classified 938 cases of coronary heart disease on the basis of occupation and concluded that there was no great occupational difference in incidence However the incidence was somewhat higher in the professional and business group than in the total series

Yater s study of a large series of Army personnel (1948) showed an association between the pre Army occupation, both rural and urban and the disease state Our group did not have the opportunity to study any individuals with coronary heart disease selected primarily because they were of rural origin most of the patients were city dwellers

In the present study we have investigated the suggestion that supervisory personnel are unduly prone to the disorder a suggestion that comes not only from Yater s series but also from Dunbar s work and our own interview data It was our impression throughout the interviews that these patients wanted to succeed in anything they attempted and furthermore that they were able to do so

The occupations of the 97 males in our series are given in detail in Appendix E (Although 13 men were in the armed forces at the time of their coronary episodes their pre service occupations were listed since in all but three cases their peacetime activity other than that of professional soldier) The distribution ajor ath
pations is given in Table 2 according to the following bro contrast to

I Executive and managerial owner and operator of re letters in
prise with policy and executive function or other coronary heart
with the supervision of the activities of others schools 10 05
II Professional physician lawyer architect and t Harvard Uni
employed and without general manageria' fur n major sports
III Semiprofessional specialty salesman medica t in the coronary
trained factory technician ajor athletics while
IV Skilled machine worker
V Semiskilled maintenance mechanic electri to semiprofessional
VI Unskilled factory worker d competitive skier

The major distinction in this classificatio fter their school days
(those in charge of others) and Classes II to ther club or Y M C A
pations are not at a managerial and direct
poration lawyer with an active staff would en the coronary condi

TABLE V–2 Occupational classifications of coronary heart disease group of 97 males

Class		No of patients
I	Managerial	42
II	Professional	11
III	Semiprofessional	7
IV	Skilled	4
V	Semiskilled	30
VI	Unskilled	3

lawyer without a staff would be in Class II A sales manager would be in Class I a salesman in Class III

It is evident from the table that the coronary heart disease group is not confined to any one occupational class The proportion of cases falling into the managerial and executive classes appears to be very high 42 out of 97 cases (There has long been a clinical impression that there is a bias in this direction) It is unfortunate that we do not have available for purposes of comparison a sample of the general male population selected in a manner similar to that of the coronary heart disease group It is believed that this inordinately large increase in managerial and executive groups is larger than one sees in the general population

This analysis points to two important facts (*a*) coronary heart disease is not confined to any one occupational class and (*b*) those in managerial and executive positions do exhibit a relatively high frequency of appearance in this series of patients It should be observed however that factors other than executive and managerial talents may augment the number of individuals holding such positions who are among the coronary patients These factors would include hereditary influences hormonal imbalances and disturbances in lipid metabolism

REFERENCES

Boas E P *Coronary Artery Disease* Year Book Publishers Chicago 1949

Boas E P and Donner S Coronary artery disease in working classes *J.A.M.A* 98 2186–2189 1932

Chisholm B Social medicine *Scient Am* 1804 11–15 1949

Gordon W H Bland E F and White P D Coronary artery disease analyzed ...idlice ... m *Am Heart J* 17 10–14 1939

...nd Brown C L Coronary thrombosis its various clinical features ...15–418 19 9

versely if a

we assume th

MASTER A M DACK S and JAFFE H L Precipitating factors of coronary artery occlusion further observations on the mode of onset of a large series of cases with particular emphasis on the role of effort and excitement *Indust Med* 8 327–331 1939

NEWMAN M Coronary occlusion in young adults *Lancet* 2 409–411 1946

WHITE P D *Heart Disease* 3rd Ed Macmillan Co New York 1944

YATER W M TRAUM A H BROWN W G FITZGERALD R P GEISLER M A and WILCOX B B Coronary artery disease in men eighteen to thirty nine years of age *Am Heart J* 36 334–372 481–526 683–722 1948

onary condi

CHAPTER VI

Findings on Masculinity

THERE is reliable evidence that human life in males is more brittle than in females (Clark 1786 quoted in Hamilton 1948) and that mere maleness influences unfavorably the resistance of the organism to disease at all ages' The selection of males for earlier demise is not restricted to human beings alone for similar observa tions have been made on many forms of animal life (Hamilton 1948)

Not only is the male selected for demise at an earlier age than the female but his greater susceptibility extends to nearly all types of ailments except those of the endocrine system (Hamilton 1948) This fact is reinforced by the startling observations that in many pathological conditions the predisposition of the male is over 85 per cent These conditions include common baldness thrombo angitis obliterans hemochromatosis gout jejunal ulcer postopera tive gastro jejunocolic fistula leucoplakia of the tongue and cancer of the inferior portion of the oral cavity (Hamilton 1948)

In studies of coronary heart disease in which there are no com plicating features like diabetes xanthomatosis or hypertension the incidence of the disease under the age of 40 is twenty four times as frequent in males as in females (Glendy Levine and White 1938 and present study) This ratio decreases with age (Gordon et al 1939)

Since coronary thrombosis was not described as a clinical entity until 1912 and since accurate diagnosis and recording of this disease as a cause of death was not done to any reliable degree until about 1940 acceptable data which could be of help in com paring the incidence of coronary heart disease in men and women are not available It is however the impression of statisticians that
andice heart disease has increased to a greater extent in men
versely if a ...en during the past 10 to 20 years (Moore 1953)
we assume th

Certain causal relations have been invoked to explain the higher incidence of coronary heart disease among males These etiological factors mav be divided into three groups (*a*) physical differences (*b*) hormonal differences and (*c*) genetic differences

There are claims that the male temperament environment and habits require a greater expenditure of energy and that this difference in energy output is primarily responsible for the higher incidence of coronary heart disease among males (Pearl 1931) Such an assumption based on differences in physical energy alone is not supported by evidence Possibly the excess of energy output is an expression of other factors that would be harmful in themselves even if the energy output could be controlled

Similarly not all the attributes of maleness that may govern predisposition to coronary heart disease need be imputed to gonadal secretions and sex hormones (see Chapter VII) These secretions maintain a highly active state of function in various tissues with resultant increase in body metabolism and influence (*a*) male behavior to some extent (Beach 1948) (*b*) steroid metabolism with specific reference to cholesterol (Sayers et al 1943) and (*c*) degree of intimal permeability However there is no definite evidence that the androgens exert any specific deleterious action on the coronary arteries

In some individuals a relative change in certain characteristics such as degree of aggressiveness submissiveness and docility does occur with the amount of androgenic material available Thus C C Hawke reports 90 male castrates studied in Kansas who were originally docile agreeable submissive and cooperative became recalcitrant disagreeable intractable and uncooperative as the daily dose of testosterone was increased

The genetic influence is considered in greater detail in Chapter III It is sufficient to say here that the hereditary aspect probably includes additional factors which may be (*a*) autosomal, (*b*) autosomal but hormonally mediated or (*c*) autosomal combined with other sex linked factors that may or may not be hormonally mediated The differentiation between sex linked and hormonally mediated disorders is sometimes difficult to determine and coronary heart disease may be one of these borderline conditions Thus the genotypes that govern predisposition to coronary hear'
may be suppressed by gynogenic hormones and evokesnary condi

genic hormones The Kansas study referred to above of 90 males who were castrated at ages varying from prepuberty to middle age may shed light on the male predisposition to coronary heart disease for these castrates are males *genetically* but *not hormonally*

Masculine and Feminine Characteristics

In evaluating masculine and feminine characteristics one could employ several lines of study such as psychological responses physical characteristics hormonal assays and others For practical purposes however none of these characteristics will produce a clear cut separation of the sexes even though the hormonal aspects of masculinity and femininity are fairly well established (see Chapter VII) and anthropologists have shown certain physical differences to exist between males and females—body build voice hair distribution and pelvic measurements

The psychological characteristics of men and women overlap to a very large extent Although it is undoubtedly true that the traits of both sexes are influenced by physical differences it has not been proved conclusively that any characteristic is wholly innate uninfluenced by training and environment So complex are the interrelations between biological and environmental factors that it is impossible in the light of present knowledge at least to say more than that men and women in our culture respond in certain general ways with statistical consistency (see Appendix A) Thus men do react more consistently with aggressiveness and women with docility but how far through innate or acquired responses we cannot say

When it comes to definitely acquired characteristics the distinction between the sexes becomes less and less apparent Thus love of fine art and music is a common meeting ground enjoyment of books dealing with intellectual interests rather than with adventure or homemaking is a mutual experience

In an effort to provide some sort of rating scale for psychological differences exhibited by men and women without attempting to evaluate the innateness of the traits revealed Terman and Miles (1936) devised a test which is useful in determining to what extent an individual fits the typically masculine or feminine pattern of our

...udance ...oth the coronary patients and their matched controls
...versely if a ... test as a part of this study
we assume thi...

Terman Miles test

The test is divided into parts A and B * each of which contains seven sections Each section contains questions word associations or other types of data that are considered to distinguish the typically masculine or feminine characteristics of an individual of either sex The typically masculine elements are scored as plus the feminine as minus and neuter as zero The average scores for male college athletes and engineers as studied by Terman and Miles are + 92 and + 77 respectively while average scores for dressmakers and grade school girls are — 104 and — 95 respectively Women holding M D and Ph D degrees scored an average of — 34 The seven exercises of the Terman Miles test are

1 Quadruple choice word associations
2 Ink blot associations
3 Information test
4 Emotional and ethical responses
5 Interests likes and dislikes
6 Personages and opinions
7 Introvertive responses

RESULTS The average scores obtained by 70 of the 97 males in the coronary heart disease group and by a matched control group of 70 males are summarized in Table 1

The coronary patient group scored significantly less (15 points lower) on the average for all seven exercises than did the matched control group In the individual exercises the coronary disease group scored significantly less in Exercises 3 and 6 Exercise 3 is the general information test a multiple choice questionnaire calling for an exact knowledge of fact that is dependent upon the experience and interests of the subject *The test revealed that the coronary heart* disease patients as a group were somewhat less aggressive, adventurous enterprising and self assertive than the control group They were actively sympathetic and concerned with domestic affairs art and literature Exercise 6 has two sections one calling for expression of attitude toward selected historical personages and the other for judgment concerning the truth or falsity of certain statements Generally speaking it may be stated that in preferring

*Usually the average sum of the scores on test A and test B is e the final score But this is not necessary since either test alon ary condi Test A was employed throughout this study

TABLE VI–1 Mean scores on Terman Miles test made by coronary heart diseas group and matched control group each of 70 males*

Exer cise	No of cases	Coronary group mean ± S E	No of cases	Control g oup mean ± S E
1	70	— 5 3 ± 1 0	70	— 7 6 ± 0 9
2	70	+ 0 2 ± 0 3	70	— 6 ± 0 3
3	70	— 0 4 ± 1 2	70	+ 9 4 ± 0 6†
4	70	+ 26 6 ± 2 8	70	+ 33 2 ± 1 8
5	70	+ 13 9 ± 1 8	70	+ 12 5 ± 1 5
6	70	+ 1 4 ± 1 0	70	+ 5 4 ± 0 6†
7	70	+ 0 4 ± 0 7	70	— 1 0 ± 0 5
TOTAL	70	+ 36 0 ± 4 7	70	+ 51 2 ± 2 8†

*27 tests in ea h group were not completed for diverse reasons
†Significantly greater

famous women unfortunate people and philanthropists rather than successful generals sports heroes and defiers of convention and by thus favoring kindly sentiments that made allowances for dis abilities such as their own our coronary patients again showed a more typically female pattern

INTERPRETATION These results may appear to be surprising in view of the fact that many of the coronary patients have been described as tending to be hard driving and determined to succeed The apparent contradiction however has several possible explana tions The very fact that these men were able to push through to success in their enterprises may well have put them in a position to participate increasingly in the more cultural aspects of our so ciety thereby modifying their interests and attitudes in the direction considered more typically feminine Furthermore at the time of testing most of the patients had experienced some degree of in validism which in itself might lead to the adoption of more sym pathetic attitudes and more sedentary and intellectual interests

One may seriously question whether the characteristics usually associated with psychological masculinity or femininity influence the susceptibility of the individual to coronary heart disease Even though we have found that the typical patient originally showed masculine traits that were later modified toward the feminine can we assume that in general overt characteristics of masculinity in a healthy male are indicative of covert characteristics which may enhance his susceptibility to coronary heart disease? And con versely if a healthy male shows overt feminine characteristics can we assume that these are indicative of covert characteristics which

may confer protection against the disease? Hamilton (1948) has stated that he avoids the often tempting but naive tendency to ascribe all conditions associated with one sex solely to the tempera ments habits or environments of the members of that sex How ever whether or not such characteristics as aggressiveness boldness and love of adventure are causally related to coronary heart disease they may possibly be expressions of some hormonal factor that may be linked intimately with the etiology of the disease

Relation of Morphological Findings to Aging and Masculinity

There were a number of suggestions that the young male prone to coronary heart disease might show (*a*) characteristics of pre mature aging or (*b*) *excessive development of masculine character* istics or excessive response to androgenic stimuli In the first case the assumption was that coronary heart disease is a concomitant of age and that therefore the individual who shows this condition at an unusually early age must be prematurely aged The second hypothesis is based on the known disproportionate ratio of males to females with coronary heart disease at this age level and it was suggested that since coronary heart disease is masculine those who have it earliest are *ipso facto* more masculine Both questions could be investigated by analyzing morphological findings Were the first suggestion true—that the young patients in our series were prematurely aged—we could anticipate excessive balding excessive graying and other concomitants of age such as arcus senilis tem poral arteritis and calcification of the aorta If the second were true—that the patients showed unusual responses to androgenic stimuli or produced unusual amounts of androgenic substances—we could anticipate excessive development of body hair musculature and so forth and a minimum of gynandromorphic characteristics Accordingly the following characteristics were rated

1 Hair graying balding, and body hair
2 Body form size of genitalia gynandromorphy pectoral develop ment thigh interspace knee interspace hip roundness waist curvature and pectoral development

Rating methods and results

SCALP HAIR Each of the items (see Figure 1 and Table 2) was rated separately on a 5 point scale ranging from a minimum of zero

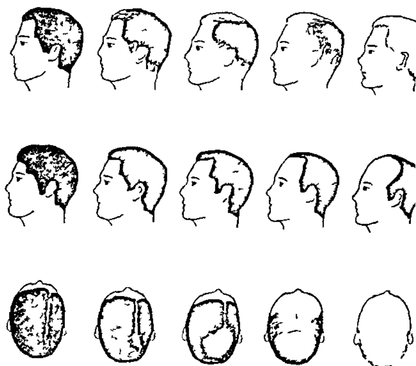


FIGURE VI–1 Hair rating five degrees of graying (*top*) frontal balding (*center*) and tonsorial balding (*below*)

TABLE VI–2 Hair rating

Item	*Rating*	*Description*
Hair graying	0–4	0 no graying or a few gray hairs 4 totally or nearly white
Frontal balding	0–4	0 no frontal notch balding 1 frontal notch balding 2 enlarged notch recession 3 near complete frontal 4 total frontal balding
Tonsorial balding	0–4	0 no tonsorial balding 1 thinness over occipital whorl 2 definite circle balding 3 enlarged circle balding 4 tonsorial "Hippocratic fringe"
Combined balding	0–8	Total of frontal and tonsorial ratings

TABLE VI-3 Percentage of coronary heart disease group of 97 males and of un matched control group of 146 males whose hair rating was 1 or more

	Coronary group %	Control group %
Graying	40	45
Frontal balding	95	95
Tonsorial balding	44	41
Combined balding	95	95

to a maximum of 4 Certain items—total balding total hair, and total areas—are totals of others and thus may have more points on the scale

Although the rating method is admittedly subjective the use of a 5 point system proved satisfactory and highly reproducible Certain ratings such as a zero or a 1 or a 4 in frontal balding can be made by any observer without previous practice (see Figure 1 and Table 2) the majority of the ratings showed high correlations between the two observers (Garn 1951)

As Table 3 shows there was no evidence of increased graying in the coronary group The chi square test indicated no differ ence in the distribution of graying Frontal balding tonsorial bald ing and combined balding showed no significant differences Hence there was no evidence that the young coronary disease population was either grayer or balder or more prematurely aged in these respects

BODY HAIR The rating employed for body hair is given in Table 4 Again a 5 point scale was used

In general findings revealed the body hair of the young coro nary heart disease group was slightly greater than that of the un matched control group but this difference was not significant in most of the regions examined In certain regions (thoracic lower arm upper arm thigh leg sacral and upper back) the greater hairiness of the coronary heart disease group almost attained sta tistical significance by the chi square test Analysis of midphalangeal hair patterns showed more individuals in the coronary than in the control group who (*a*) had no such hair (45 3 per cent versus 37 7 per cent) and (*b*) had more hair on the fourth finger alone (18 9 per cent versus 12 3 per cent) By and large however these facts merely reflect a greater percentage of Mediterranean peoples in the coronary group (Bernstein and Burke 1942)

TABLE VI–4 Body hair rating

Item	*Description*
Beard	0 absent
	1 mustache chin beard
	2 mustache chin beard cheek beard
	3 mustache chin beard cheek beard (heavy)
	4 extends to intraorbital region
Abdominal	*0 absent*
	1 linea alba triangle
	2 spread
	3 over rectus to costal angle
	4 covering rectus obliques to sides
Thoracic	0 absent
	1 circum areola or sternal
	2 spread over chest nearly to deltoids
	3 axilla
	4 total to deltoids and axilla
Lower leg arm	0 absent
	1 over dorsal aspects only
	2 spread lightly
	3 dorsal same ventral hands
	4 total all aspects feet and hands
Upper leg arm	0 absent
	1 slight dorsal
	2 marked development
	3 nearly to hips shoulders
	4 total coverage to deltoids and gluteal region
Gluteal	0 absent
	1 anal cleft
	2 extended
	3 skin nearly covered
	4 total dense
Sacral	0 absent
	1 few hairs
	2 marked
	3 marked triangle
	4 dense
Lower back	same ratings as for Sacral
Upper back	same ratings as for Sacral
Midphalangeal	individual fingers noted
Total hair	total of all above ratings (0–40)
Total areas	no of areas rated 1 or more (0–10)

TABLE VI-5 Body hair in coronary heart disease group of 97 males and unmatched control group of 146 males

	Coronary group Mean ± S E	Mod	Control group Mean ± S E	Mode	Difference	Significance	Chi square
Total of body hair ratings	12 80 ± 7	12	11 30 ± 7	8 10	+ 1 50	1 5 n s	*
No of areas in which hair was observed†	6 90 ± 2	6	6 10 ± 2	6	+ 80	2 8*	

N s —Not significant
*Significant
†Beard abdominal thoracic lower arm, upper arm thigh leg, gluteal sacral, lower back, and upper back.

When the scores for all ten areas were totaled the average was 12 80 for the coronary heart disease group and 11 30 for the unmatched controls (see Table 5) The difference is suggestive but not clearly significant

Of the ten areas examined the average number scoring 1 or more in the coronary heart disease group was 6 9 and for the control group 6 1 Again the difference was suggestive but not clearly significant

BODY FORM In distinction to the rating of hair, the characteristics of body form were rated on a 4 point scale

TABLE VI-6 Body form rating

Item	Description
Gynandromorphic index	Feminoid appearance in general configurations
Texture index	(See Sheldon 1940)
Thigh interspace	Degree of thigh juxtaposition 1 no space 4 maximum space
Knee interspace	1 no space 4 maximum space
Hip roundness	1 narrow or straight hips 4 broad round hips
Waist curvature	Incurvation of waist 1 minimum 4 maximum
Pectoral development	Fatty development over pectoral region 1 no fatty development 2 slight softness 3 mammary development 4 distinct breast formation

There were a number of differences in detailed *morphological* characteristics between the coronary heart disease group and the unmatched control group but these differences which appeared to be spotty and form no regular pattern tended to be explained as partial functions of the somatotype

In the broader aspects of body form significant differences between the two groups were found in the following variables texture index thigh interspace knee interspace hip roundness waist curvature and pectoral development These findings are summarized in Table 7

The coronary heart disease patients were found to have slightly finer texture and slightly rounder hips The slight excess of hip roundness they displayed may be explained by the marked deficiency in ectomorphy and the excess of endomorphic mesomorphy in the coronary group

Similarly the lower degree of ectomorphy in the coronary heart disease group can account for less knee and thigh interspace as compared with the control group It is the ectomorph and the mesomorphic ectomorph who have the cowboy legs

The increased mesomorphy in the coronary group apparently also resulted in less waist curvature than was shown by the control group

Hence the following differences may be attributed to higher mesomorphy in the coronary heart disease group (*a*) less thigh interspace (*b*) less knee interspace (*c*) more hip roundness and (*d*) less waist curvature

TABLE VI–7 Body form in coronary group of 97 males and unmatched control group of 146 males

	Coronary group mean ± S.E	*Control group mean ± S.E*
Gynandromorphic index	1 29 ± 07	1 19 ± 04 n.s
Texture index	2 26 ± 10	2 01 ± 06*
Thigh interspace	1 48 ± 11	1 76 ± 07
Knee interspace	1 41 ± 11	2 1[illegible] ± 07†
Hip roundness	1 38 ± 08	1 17 ± 04
Waist curvature	77 ± 09	1 10 ± 03†
Pectoral development	95 ± 08	1.37 ± 05†

N s —Not significant.
Significant.
†Highly significant.

Summary

Why is the male more prone to coronary heart disease? Does masculinity predispose toward the disease? If so, how is masculinity to be assessed? The problem is complicated by the necessity of choosing characteristics which will permit comparison of discernible degrees of difference Is the appraisal to deal with hormonal makeup that is the excess of testosterone in the male? Can the evaluation be based on body build? Or can masculinity be measured in psychological terms by determining differences in attitudes? These questions were considered in making our study No definitive answers emerged but several findings are noteworthy

In relation to hormonal makeup there was no evidence that excessive androgens predispose toward or produce coronary heart disease

In morphological makeup the study indicated the coronary patients were more masculine than the controls

Psychologically the coronary group showed attitudes that are considered more typically feminine than those of the control group A possible explanation for the apparent conflict of this finding with the masculinity of physique is that both the cultural milieu into which the typical drive of these men may take them and the physical inactivity enforced by their illness may modify their outlook in a more cultural and sympathetic direction

Thus it may be suggested that the coronary individual studied in this group is a male with a high component of physical masculinity that is probably due to inherited characteristics but whose mental attitudes are tempered either by illness or by the acculturation to which he is exposed by virtue of his driving psychological makeup

REFERENCES

BEACH F A *Hormones and Behavior A Survey of Interrelationships Between Endocrine Secretions and Patterns of Overt Response* Harper New York 1948

BERNSTEIN M M., and BURKE B S The incidence and Mendelian transmission of mid-digital hair in man *J Hered* 33 45–53 1942

GARN S M Types and distribution of the hair in man *Ann New York Acad Sc* 53 498–507 1951

GLENDY R E LEVINE S A and WHITE P D Coronary disease in youth comparison of 100 patients under 40 with 300 persons past 80 *J.A.M.A* 109 1775–1781 1937

GORDON W H BLAND E F and WHITE P D Coronary artery disease analyzed post mortem with special reference to the influence of economic status and sex *Am Heart J* 17 10–14 1939

HAMILTON J B The role of testicular secretions as indicated by the effects of castration in man and by studies of pathological conditions and the short life span associated with maleness *Recent Prog in Hormone Research* 3 257–322 1948

MOORE F National Institute of Health Personal communication

PEARL, R Studies on human longevity IV The inheritance of longevity *Human Biol* 3 245–269 1931

SAYERS G SAYERS M A WHITE A and LONG C N H Effect of pituitary adrenotropic hormone on cholesterol content of rat adrenal gland *Proc Soc Exp Biol and Med* 52 200–202 1943

SHELDON W H STEVENS S S and TUCKER W B *The Varieties of Human Physique* Harper & Bros New York 1940

TERMAN L M and MILES C C *Sex and Personality* McGraw Hill New York 1936

CHAPTER VII

Endocrine Findings

THE hormonal aspects of masculinity have been the subject of broad and intensive studies by Allen (1934) Hamilton (1948) and others The present study at first aimed simply to assess the hormonal aspect of masculinity by a survey of urinary 17 ketosteroid excretion Although this was known to provide a very crude estimate of androgenic activity it was believed that any deviation from the expected norm in the amount of daily excretion might suggest a parallel change in androgenic secretion by the adrenals and the testes This is discussed at greater length later in the chapter

In addition however another aspect of hormonal appraisal was carried out determination of thyroid status This was appraised by means of (*a*) basal metabolic rate (*b*) radioactive iodine urinary excretion and (*c*) various serum lipid interrelations Since coronary heart disease is more common in individuals with hypercholesterolemia and since hypercholesterolemia and hypothyroidism are often associated it was decided to determine the degree and extent of thyroid influence on this elevated level of serum cholesterol

17 Ketosteroids

The measurement of androgenic and estrogenic material by biological tests is not sufficiently specific to be entirely satisfactory (Fraser et al 1941) However this difficulty was partially overcome by Callow's modification of the Zimmerman technique of determining 17 ketosteroids It should be emphasized that not all androgens are chromogenic and conversely, not all chromogenic materials possess androgenic activity For example etiocholane 17 one 3 α ol is a 17 ketosteroid but not an androgen while testosterone is an androgen but not a 17 ketosteroid The chromogenic reaction and hence chemical specificity of the 17 ketosteroids depends upon a property of the grouping (CH CO) containing an

active methylene group on the carbon at position 17 of the steroid nucleus namely the ability to produce in the presence of meta dinitrobenzene a red color which may be analyzed quantitatively by the use of a photoelectric colorimeter with a green filter having a maximal transmission at 5120 Å

The 17 ketosteroids (sterone) are part of the metabolic products of both the adrenal and testicular glandular secretions excreted in the urine The values considered normal for male adults vary from 6 mg to 22 mg of sterone per 24 hour urinary excretion while the values for females are lower (5 mg to 15 mg of sterone per 24 hour urinary excretion) The most difficult problems in this determination today are (*a*) fractionation of all the steroids excreted in the urine that possess androgenic activity and (*b*) differentiation of the amounts of androgens excreted by the adrenal cortex and by the testes

No attempt was made in this study to fractionate the urine either into androgenic material or the alpha and beta ketosteroids as has been done by Salter et al (1946) or Hamilton and Hamilton (1948) Accordingly this study will give no insight into the adrenal as compared with the testicular contribution of the 17 ketosteroid excretion

The values of the urinary sterone of 87 males who had experienced coronary heart disease are listed in Table 1 The influence of chronic debility on 17 ketosteroid excretion in the coronary heart disease patients is probably not an important factor since these patients are not debilitated in the usual sense of the word and are not the usual chronically ill type Although they have experienced an illness they have made a good recovery so far as muscle tonus and general physical welfare are concerned (Barrabee 1950) The sterone excretion in the coronary heart disease group in Tables I and 2 and Figure 1 is compared with that of a healthy group compiled by Dr Fuller Albright and Dr Anne P Forbes in the Massachusetts General Hospital These controls were laboratory assistants physicians normal soldiers and several members of the maintenance staff of the hospital The data are comparable with ours the determinations having been made by the same laboratory The average age of the 87 men in the coronary group who had 17 ketosteroid determinations was 36 4 years and of the 50 in Albright and Forbes control group 28 4 years

From the data included in Table 1 it is interesting to note that the difference between the mean 24 hour urinary sterone excretion of the coronary group and that of the control group is not significant in spite of the difference of approximately ten years in average age If the data for the coronary heart disease group were corrected for age using the information in Table 2 the difference between the means would be even less

Relation to age

There is evidence to suggest that the 17 ketosteroid urinary excretion begins to decrease at the age of 30 (Hamilton and Hamilton 1948 Venning and Kazmin 1946) Furthermore Hamilton and Hamilton state *

> The major part of this decline is due to a loss of alpha ketosteroids which accounts in general for over 90 per cent of the total quantity of urinary ketosteroids The curve of decrease in alpha ketosteroids parallels closely that for the total output of ketosteroids

Our results shown in Table 2 are consonant with these observations there is a significant decrease in 17 ketosteroid excretion during the course of the fourth and fifth decades

Relation to other variables

The 17 ketosteroids are closely involved with many other variables in the human organism both in the normal and in the diseased state (Dobriner et al 1948) It seemed advisable to establish if possible the relations of the urinary ketosteroids to other variables examined during the course of this study The correlation coefficients ranged from — 19 to + 19 None were statistically significant They included correlations between 17 ketosteroids and age height weight ponderal index endomorphy mesomorphy ectomorphy uric acid phospholipids cholesterol basal metabolic rate and gynandromorphy Those approaching significance were age (— 19 ± 11), basal metabolic rate (+ 19 ± 11) and gynandromorphy (— 19 ± 11)

The correlation between 24 hour urinary 17 ketosteroid excretion and endomorphy mesomorphy and ectomorphy was further investigated by comparing the 24 hour urinary sterone excretions

*Howard B Hamilton and James B Hamilton "Ageing in Apparently Normal Men" *J Clin Endocrinol* 8 451 1948

TABLE VII–1 24 hour urinary sterone excretion in coronary heart disease group of 87 males* and control group of 50 healthy males (Albright and Forbes series)

Sterone m †	*Co onary g oup*	*Cont ol group*
	No	*No*
2	1	0
3	4	0
4	5	1
5	5	3
6	4	3
7	6	2
8	8	7
9	13	7
10	10	5
11	9	5
12	8	3
13	3	3
14	1	3
15	1	2
16	2	3
17	3	2
18	1	0
19	1	0
20	1	0
21	1	1
	Ste one mg	*Sterone mg*
Mean	9 9	11 1
Standard deviation	4 2	3 7
Range	2 4–21 0	4 9–21 6
Standard error	0 44	0 54

Urinary excretion of sterone was not measured in 10 male patients
†Amounts are given to the last whole milligram.

TABLE VII–2 24 hour urinary sterone ex retion by age decades in coronary heart disease group of 87 males and control group of 50 healthy males (Albright and Forbes series)

Ag decade	*No of cases*		STERONE, MG *Ran e*	*Mean ± SE*
20–29	Coronary	6	3 9–18 5	11.5 ± 2 36
	Control	27	5 4–21 6	12.2 ± 0 85
30–39	Coronary	49	4 1–21 0	10 7 ± 0 57
	Control	19	4 9–19 6	11 6 ± 1 1-
40–49	*Coronary*	32	2 4–15 0	8 6 ± 0.56
	Control	4	5 6–18 5	11 2 ± 1 90

Urinary excretion of sterone was not measured in 10 male patients.

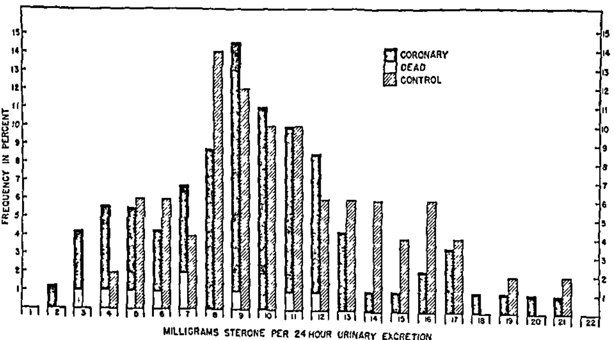


FIGURE VII-1 24 hour urinary sterone excretion by 87 coronary heart disease patients and 50 unmatched controls
It is to be noted that those in the coronary group who died showed on the whole lower sterone excretion than those who survived (see also Table 4)

TABLE VII–3 24-hour urinary sterone excretion by physique in coronary heart disease group of 87 males*

Predominant physique	*No of cases*	*Ste one mg m an ± S E*
Endomorphy	21	9 98 ± 0 95
Mesomorphy	39	10 56 ± 0 66
Ectomorphy	8	8 88 ± 1 35
Mid range	19	9 25 ± 0 77

Urinary excretion of sterone was not measured in 10 male patients

for the individuals in these three classifications However as might be anticipated from the other correlations no significant differences were found The exact values are listed in Table 3

Relation to death in coronary patients

The values of urinary 17 ketosteroids were obtained in 9 men and 1 woman approximately two to four months prior to their deaths The woman patient had a 24 hour 17 ketosteroid excretion of 2 2 mg The values for the 9 men are listed in Table 4 (see also Figure 1)

It is noteworthy that in the coronary heart disease group the difference between the means of the surviving males (10 1 ± 42) and of the males who died (7 68 ± 1 02) is just barely significant The decrease in 17 ketosteroids is interesting and merits further attention The exact mechanism of this decrease will be unknown until better methods are available for distinguishing whether the components of the 17 ketosteroid fraction are adrenal or testicular in origin

TABLE VII–4 24-hour urinary sterone excretion of 9 males who died from coronary heart disease

Case no	*Ste one mg*
17	12 5
31	7 8
38	3.9
47	7 3
49	11 8
63	4 1
64	5 8
69	9 3
71	6 6
Mean ± S E.	7 68 ± 1 02

Summarv

The average 24 hour urinary sterone excretion in 87 young coronary patients was found to be lower arithmetically but not to a statistically significant degree, than that of 50 healthy controls who were on the average ten years younger the means and standard errors being 9 9 ± 0 44 mg per cent and 11 1 ± 0 54 mg per cent This fact is interesting in that one would expect a significantly lower 24 hour sterone excretion in the coronary group on the basis of age alone for it is fairly well accepted that sterone excretion decreases with age On the other hand, if any true alteration in sterone excretion accompanied coronary heart disease the average differences would be even greater with the coronary heart disease group showing an even lower daily sterone excretion This point should not be dismissed lightly in pite of the age difference between the groups the average dailv sterone excretion of both groups was nearly the same

Those in the coronary group who died revealed a lower mean daily sterone excretion than those who were living at the time of this appraisal 7 68 ± 1 02 (p = 0 05) as against 10 1 ± 42 mg per cent

These findings may be of some value in providing an objective basis for the assessment of the status of the patient following a myocardial infarction If these data are substantiated by further follow up and study the method may prove to be much more objective and useful than any now employed A routine periodic survev of 24 hour urinarv sterone excretion would enable the physician to follow changes in the excretion pattern and if it showed a perceptible decrease then it theoretically should be possible to institute replacement therapy even if the classical ominous symptoms of coronary heart disease were not apparent

The interrelations between daily urinary sterone excretion and other attributes such as age basal metabolic rate various physical components and biochemical variables were found to be statistically insignificant on the basis of coefficient correlation data although certain coefficients of correlation approached significance namely those of age gynandromorphy and basal metabolic rate which were found to be — 19 ± 11 — 19 ± 11, and + 19 ± 11 respectively

Thyroid Function

There has been little published in medical literature concerning the thyroid status in coronary heart disease Blumgart et al (1933 1950) have attempted to produce a state of hypothyroidism by means of total ablation or radioactive iodine in order to improve the cardiac status in coronary or myocardial insufficiency by decreasing the cardiac output and hence the work of the heart In 1946 J Lerman and P D White suggested that the thyroid status of coronary heart disease patients under the age of 40 tends generally to be in the direction of a low basal metabolic rate Since their series was small and further tests confirming this initial impression were desired by Lerman and White additional studies on the thyroid aspects of coronary heart disease were incorporated in the present general study Starr et al (1934) studied 8 patients (3 of whom were females all in the seventh decade) but their series is also too small to merit evaluation

The thyroid status may be gauged by means of various tests The question of which is the best test has not been answered clearly Probably Means (1948) has best epitomized the situation *

To say that any one of these procedures is better or worse than another as an index of thyroid function is meaningless They measure different things Each throws light on thyroid function but from different angles

Basal metabolic rate may be said to be an index of the total impact of thyroid hormone upon all its end-organs Level of protein bound iodine is an expression of thyroid hormone concentration in the blood Uptake of labeled iodine is an index of the thyroid gland s avidity for *that element*

The values of the blood lipid levels in hypothyroidism and in hyperthyroidism have been the subject of discussion for many years In general it is stated that serum cholesterol rises during hypothyroidism and decreases during hyperthyroidism (Mason et al 1930) However the observation on this point by Peters and Man (1943) is noteworthy They accept but modify Mason s dictum †

Although cholesterol rises when the thyroid gland is removed and

J H Means *The Thyroid and Its Diseases* 2nd ed J B Lippincott Co Philadelphia 1948 p 167 Quoted by permission of the publishers

†John P Peters and Evelyn B Man "The Interrelations of Serum Lipids in Patients with Thyroid Disease" *J Clin Invest* 22 719 Sept., 1943

falls when active thyroid preparations are given normal concentrations of cholesterol may be found in the serum of patients with hyperthyroidism or with thyroid deficiency because the level to which cholesterol falls or rises with these disorders is roughly related to the normal cholesterol concentration of the affected subject

An excellent work on the interrelation of the lipids in hyperthyroidism and hypothyroidism is that of Foldes and Murphy (1946) In general they confirmed Mason s observations and extended them to include other lipids Thus plasma cholesterol cholesterol esters and phospholipids were found to be significantly increased in hypothyroidism The cholesterol esters/total cholesterol and total cholesterol/lipid phosphorus ratios were significantly increased In hyperthyroidism these changes were not so constant or significant The plasma phospholipids were decreased significantly, cholesterol and cholesterol esters were decreased absolutely

This study has adopted Means principle in assessing thyroid function namely the use of multiple tests of which the following were employed basal metabolic rate radioactive iodine urinary excretion and serum lipid constituents including serum cholesterol (total and esters) serum lipid phosphorus total cholesterol/lipid phosphorus ratio and cholesterol esters/total cholesterol ratio (discussed in Chapter VIII) The use of the lipids as an index of thyroid activity is open to question for it is not known whether the changes in serum lipids are solely characteristic of individuals prone to coronary heart disease or whether they are in part the result of change in thyroid function For these reasons less reliance was placed on the serum lipids than on the basal metabolic rate and radioactive iodine excretion

Basal metabolic rate

The basal metabolic rate was obtained in 87 coronary patients on the morning after admission to the hospital Thus all rates were determined under the most favorable conditions using standardized procedure in the metabolic laboratory at the Massachusetts General Hospital

Table 5 shows the percentages by which the basal metabolic rates of the 87 patients varied from a standard mean

The mean basal metabolic rate in the coronary heart disease group is certainly shown to vary on the low side of accepted normal

TABLE VII–5 Percentage of variation from standard mean basal metabolic rate in coronary heart disease group of 87 males*

Percentage of variation	No of patients
—30 to —26	4
—25 to —21	11
—20 to —16	14
—15 to —11	20
—10 to — 6	17
— 5 to — 1	14
+ 1 to + 5	4
+ 6 to + 10	2
+ 11 to + 15	1
Mean ± standard error —12 ± 9	
Range —30 to + 12	

In 10 males and 3 females the basal metabolic rate record was unsatisfactory or incomplete

values for the general population It is possible for a low metabolic rate to result from (a) depressed secretion of the thyroid gland (thyroxin) (b) depressed secretion of thyrotropic or other endocrine hormones or (c) failure of the end organs in either the body or the thyroid to respond to thyroxin or to thyrotropic hormone respectively It must be considered however whether the low values recorded for the coronary group actually reflect a low metabolic rate or are the result of the method of calculation The basal metabolic rate—the amount of energy expended under basal conditions—is expressed in terms of body heat as measured by oxygen consumption in relation to time and to surface area The standards of oxygen consumption against which individual rates are measured have been determined empirically taking into account the variables of age sex and surface area in a limited number of normal persons Of these variables the major one is surface area to which there are several theoretical objections Since surface area is computed from height and weight there is bound to be some error especially in the shortest and tallest individuals whose weight is often out of proportion to their height This fact has a bearing on our data for in the coronary heart disease group height was significantly less and lateral measurements were greater than in the general population (see Chapter IV) resulting in weight disproportionate to height We believe therefore that the variation

of — 12 per cent from the standard basal metabolic rate shown by these patients may be normal for their type of physique

The coefficients of correlation between basal metabolic rate and variables such as uric acid urinary 17 ketosteroids, and various lipids ranged from + 09 to + 19 none were statistically significant The coefficients of correlation between basal metabolic rate and age and weight were — 10 and — 16 respectively, also not significant

Radioactive iodine

As stated previously the uptake of administered radioactive iodine measures the avidity of the thyroid gland for iodine Hertz Roberts and Evans (1938) showed that labeled iodine is concentrated by the thyroid in amounts many times greater than by any other tissue of the body This principle has been extended to the study of abnormal thyroid physiology and, specifically to the hyperthyroid and hypothyroid states

Essentially the technique adopted in the Massachusetts General Hospital and employed in the study of 21 of our patients is as follows The patient is given 100 cc of a solution containing 100 microcuries of radioactive iodine 131 (half life 8 days) and 100 micrograms of sodium iodide (as a carrier) A small aliquot is taken as a standard Urine is then collected for 48 hours Usually two 24 hour specimens are obtained however we have collected the specimens for 48 hours in two 6 hour specimens one 12 hour specimen and one 24 hour specimen

The three extreme ranges of thyroid function are given as follows (Rawson et al, 1949)

1 Euthyroid 53–84 per cent excretion in 48 hours
2 Thyrotoxic 8–32 per cent excretion in 48 hours
3 Myxedematous 74–93 per cent excretion in 48 hours

Radioactive iodine excretion by the 21 coronary patients revealed a slight downward change from the euthyroid state (see Figure 2) The percentage of radioactive iodine excreted in the urine in 48 hours ranged from 47 to 80 with an average of 60 While it is known that this test is not as critical in evaluating the thyroid status as an analysis of the blood iodine levels it is nevertheless satisfactory and informative for the purpose of the present study

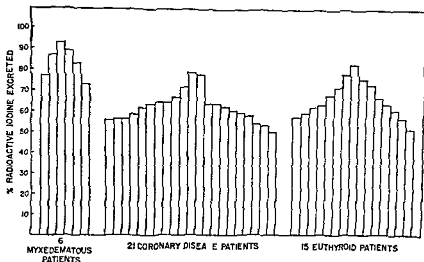


FIGURE VII–2 Per cent of radioactive iodine excreted in the urine in 48 hours by 6 myxedematous patients 21 coronary heart disease patients and 15 euthyroid patients The coronary patients showed a pattern similar to that of the euthyroid patients both these groups showed lower radioactive iodine excretion than the myxedematous group (Modeled after Rawson et al)

Serum lipid constituents

The study of serum cholesterol (free esters and total) serum lipid phosphorus and total cholesterol/lipid phosphorus ratio substantiates the evidence of the low basal metabolic rate that there is a slight change from the euthyroid state in coronary heart disease toward the hypothyroid state

The average serum total cholesterol in coronary heart disease in our series was 286 mg per cent serum cholesterol esters were 177 mg per cent and serum lipid phosphorus was 12 6 mg per cent While these values are significantly lower than the values reported in known hypothyroid states by Foldes and Murphy (1946) they are significantly higher than normal values (see Chapter VIII) The total cholesterol/lipid phosphorus ratio is significantly higher in the hypothyroid state than in the euthyroid state in this respect the coronary heart disease group was again intermediate between euthyroidism and hypothyroidism

It is interesting that the three factors—serum total cholesterol serum lipid phosphorus and total cholesterol/lipid phosphorus ratio—are increased in both the hypothyroid and the coronary heart

disease states The essential difference is the degree of increase In hypothyroidism the serum total cholesterol rises to inordinately high levels while the serum lipid phosphorus does not rise proportionately a fact which accounts for the high total cholesterol/lipid phosphorus ratio In coronary heart disease, the serum cholesterol is moderately increased and the serum lipid phosphorus is slightly increased resulting in a moderate elevation of the total cholesterol/lipid phosphorus ratio

It is of further interest that there was no significant correlation between basal metabolic rate and serum total cholesterol This fact could be interpreted as meaning that serum total cholesterol and basal metabolic rate are independent variables in the presence of the serum lipid abnormalities in coronary heart disease In hypothyroidism there is a high negative correlation between basal metabolic rate and serum total cholesterol

The rise and fall of serum total cholesterol in hypothyroidism and hyperthyroidism respectively suggest that there is an inverse relationship between serum total cholesterol and oxygen consumption (Epstein and Lande 1922) In such conditions as Addison s disease and starvation when oxygen consumption is low however it is found that, contrary to expectation low values of cholesterol are found in the serum Cutting et al (1934) showed that in *normal individuals while dinitrophenol raised the basal metabolism* (oxygen consumption), it did not affect the serum total cholesterol

Interpretation of 17 Ketosteroid and Thyroid Studies

Since coronary heart disease is predominantly a male disease, and since ketosteroids are a crude estimate of androgenic activity it was thought that the coronary heart disease group might show an increased urinary sterone excretion On the other hand since coronary heart disease is sometimes *considered a chronic disease* in the sense that once an individual has experienced it he is advised to curtail his usual activities it would not have been surprising to find a lower 17 ketosteroid excretion

The results of the study suggest a decrease in urinary sterone excretion in the coronary group It is noteworthy that the sterone excretion was decreased to a greater degree in those who died from coronary heart disease This observation raises two questions (*a*) Would a periodic *follow up of the urinary sterone excretion be*

worth while in the coronary group? (*b*) If during a follow up study the sterone excretion decreased would it benefit the patient to reverse this trend by androgen replacement therapy? Further study is needed on these points

The study of basal metabolic rate indicated that it may not provide a basis for definite evaluation of the thyroid status of the coronary group The rate is lower than that considered normal, but it has been shown that this apparent deviation may be in large part associated with the physique of the patients rather than with any decrease in oxygen consumption due to disease The study of urinary radioactive iodine excretion interrelations of the lipids and coefficients of correlation between various factors however suggests that there is some degree of functional alteration in the thyroid gland in the direction of hypothyroidism The bearing of this alteration on the genesis of coronary heart disease is not immediately apparent but in view of the known virtual absence of the disease in hyperthyroid states it is reasonable to suggest that the thyroid probably plays a role albeit minor in the genesis of the disease

REFERENCES

ALLEN E V Relationship of sex to disease *Ann Int Med* 7 1000–1012 1934

BARRABEE E Personal communications 1950

BLUMGART H L FREEDBERG A S and KURLAND G S Further experience with radioactive iodine in the treatment of euthyroid cardiac patients with angina pectoris and congestive heart failure *Proc New England Cardiovascular Society* March 1950

BLUMGART H L LEVINE S A and BERLIN D D Congestive failure and angina pectoris therapeutic effect of thyroidectomy on patients without clinical or pathologic evidence of thyroid toxicity *Arch Int Med* 51 866–877 1933

CUTTING W C RYTAND D A and TAINTER, M L Relationship between blood cholesterol and increased metabolism from dinitrophenol and thyroid *J Clin Investigation* 13 547–552 1934

DOBRINER K LIEBERMAN S and RHOADS C. P Studies in steroid metabolism I Methods for the isolation and quantitative estimation of neutral steroids present in human urine *J Biol Chem* 172 241–261 1948

EPSTEIN A A and LANDE H Studies on blood lipoids I The relation of cholesterol and protein deficiency to basal metabolism *Arch Int Med* 30 563–577 1922

FOLDES F F and MURPHY A J Distribution of cholesterol cholesterol esters and phospholipid phosphorus in blood in thyroid disease *Proc Soc Exper Biol & Med* 62 218–223 1946

FRASER, R W FORBES A P ALBRIGHT F., SULKOWITCH H and REIFENSTEIN E. C JR Colorimetric assay of 17 ketosteroids in urine a survey of the use of

this test in endocrine investigation diagnosis and therapy *J Clin Endocrinol* 1 234–256 1941

HAMILTON H B and HAMILTON J B Ageing in apparently normal men I Urinary titers of ketosteroids and of alpha hydroxy and beta hydroxy ketosteroids *J Clin Endocrinol* 8 433–452 1948

HAMILTON J B The role of testicular secretions as indicated by the effects of castration in man and by studies of pathological conditions and the short life span associated with maleness *Recent Prog Hormone Research* 3 257–322 1948

HEARD R D H Discussion at A A A S symposium on steroids at Mont Tremblant Sept 1945

HERTZ S ROBERTS A and EVANS R D Radioactive iodine as indicator in study of thyroid physiology *Proc Soc Exper Biol & Med* 38 510–513 1938

LERMAN J and WHITE P D Metabolic changes in young people with coronary heart disease *J Clin Investigation* 25 914 1946

MASON R L HUNT H M and HURXTHAL L M Blood cholesterol values in hyperthyroidism and hypothyroidism—their significance *New England J Med* 203 1273–1278 1930

MEANS J H *The Thyroid and Its Diseases* 2nd ed J B Lippincott Co Philadelphia 1948

PETERS J P and MAN E B The interrelations of serum lipids in normal persons *J Clin Investigation* 22 707–714 1943

PETERS J P and MAN E B The interrelations of serum lipids in patients with thyroid disease *J Clin Investigation* 22 715–719 1943

RAWSON R W SKANSE B N MARINELLI L D and FLUHARTY R G Radioactive iodine its use in studying certain functions of normal and neoplastic thyroid tissue *Cancer* 2 279–292 1949

SALTER W T CAHEN R L and SAPPINGTON T S Urinary 17 ketosteroids in metabolism II Partition of gonadal and adrenocortical hormonal derivatives of normal endocrine and cancerous patients *J Clin Endocrinol* 6 52–76 1946

SELTZER C C Body build and oxygen metabolism at rest and during exercise *Am J Physiol* 129 1 13 1940

STARR I JR DONAL J S MARGOLIES A SHAW R COLLINS L H and GAMBLE C J Studies of heart and circulation in disease estimations of basal cardiac output metabolism heart size and blood pressure in 235 subjects *J Clin Investigation* 13 561–592 1934

TALBOT N B Discussion at A A A S symposium on steroids at Mont Tremblant Sept 1945

VENNING E H and KAZMIN V Excretion of urinary corticoids and 17 ketosteroids in the normal individual *Endocrinology* 39 131–139 1946

CHAPTER VIII

Biochemical Findings The Interrelations of *Serum Lipids*

HISTORIANS claim that Pouletier de la Salle circa 1769 first called attention to a substance in gallstones that is soluble in alcohol and that forms crystals upon evaporation (Bills 1935) Chevreul in 1824 repeated these experiments and named the substance cholesterol (*chole* bile *steros* solid) Denis (1830) is credited with being the first to report that blood serum contains cholesterol

Although the chemical formula of cholesterol $C_{27}H_{46}O$ was suggested by Reinitzer in 1888 the molecular structure has been a subject of controversy for many years (Schoenheimer 1926) However through the efforts of many investigators the structure has been accepted subject to change as a phenanthrene cyclopentane or cholane form of sterol ring

Possibly the earliest association between cholesterol and atherosclerosis was Vogel s observation in 1847 that cholesterol is present in atherosclerotic lesions Windaus analyzed various diseased aortae in 1910 and reported six times as much cholesterol and twenty times as much cholesterol ester in atherosclerotic aortae as were observed in normal aortae Schoenheimer (1928 1934) and others extended these observations and concluded after performing chemical analyses of many aortae that the proportion of lipids in the aorta increases with age and atherosclerosis

From these observations investigators both clinical and experimental almost concurrently began to study the interdependence of *the level of serum cholesterol and the degree of atherosclerosis* Experimentalists led by Anitschkow and Chalatow (1913) produced atherosclerosis in the rabbit by feeding the animal large quantities of cholesterol Clinicians attempted to learn whether the incidence of atherosclerosis in the population with hypercholesterolemia was higher than in the normal population Thus indi

viduals with hereditary hypercholesterolemia (Boas et al 1948), nephrosis (Bloor, 1917), hypothyroidism (Epstein and Lande, 1922) xanthomatosis (Thannhauser, 1940) and diabetes mellitus (Rabinowitch 1935 Joslin et al 1917) were studied in order to ascertain the incidence of atherosclerosis

Both methods of approach have had their strong opponents and proponents Duff (1935) objected to Anitschkow s conclusions on the grounds that cholesterol an animal sterol may have an effect as an unnatural factor in an herbivorous diet that it would not necessarily have in the diet of human beings which commonly includes animal sterols Leary (1949) on the other hand disagreed with Duff and came to the same conclusions as Anitschkow after repeating and confirming Anitschkow s experiments and after studying human autopsy material with a polarizing microscope

There is no satisfactory evidence that entirely confirms or denies a causal relation between the state of hypercholesterolemia and atherosclerosis Lande and Sperry (1936) maintained from their clinical analysis of human autopsy material that no relation exists between hypercholesterolemia and atherosclerosis The association between hypercholesterolemia and cardiovascular diseases has been denied by several investigators (Page Kirk and Van Slyke 1936 Elliot and Nuzum 1936) However the bulk of the evidence is in favor of an association (Mjassnikow 1926 Davis Stern and Lesnick, 1937 Barker 1939 Poindexter and Bruger 1938 Morrison et al 1948 Steiner, 1948) Nevertheless the evidence for the existence of a higher incidence of atherosclerosis in individuals who have diseases that manifest a hypercholesterolemia cannot be accepted as concrete evidence of a causal relation, there is the possibility that atherosclerosis and hypercholesterolemia are both the end products of an altered metabolic state This possibility is further strengthened by Lerman and White s observations (1946) that in those who have experienced myocardial infarction prior to the age of 40 the serum cholesterol is higher and the basal metabolic rates are lower than in suitable controls Steiner and Kendall (1946) extended this finding and experimentally produced atherosclerosis in dogs by the addition of thiouracil and cholesterol to their usual diet Steiner s work confirmed Shapiro s observations that thyroidectomy and other alterations of the glandular state favor the development of atherosclerosis (Shapiro 1927) Thus

it is reasonable to suggest that atherosclerosis may be the end result of the combination of altered biochemical and hormonal metabolism probably caused by a local vascular fault or strain and not necessarily the result of any one factor such as an elevated serum cholesterol Blumgart (1950) has found upon examination of human cases of long standing hypothyroidism (created by subtotal thyroidectomy in 1933) that the degree of atherosclerosis is not significantly greater than is usually obtained for those in the same age group This observation causes one to question the clinical belief that hypothyroidism predisposes to atherosclerosis However Blumgart s particular cases perhaps have not lived long enough to develop atherosclerosis in spite of hypothyroidism In addition Blumgart s cases usually receive some thyroid medication which may in itself be protective against atherosclerosis

Lipid Values

In the present study in addition to the determination of the absolute level of serum total cholesterol in the coronary heart disease group and a matched control group of healthy men the question of the influence on the level of serum total cholesterol of such factors as age weight, body build and diet was considered and interpreted with particular reference to the range of the normal level and its etiologic relation to coronary heart disease Since cholesterol has been shown to be only one of the variables concerned in the etiology of coronary heart disease other lipids such as phospholipids were also determined in both groups Furthermore the interrelations of the various lipids were also considered because of the current viewpoint that the colloidal state of all the substances within the serum is more important than any one individual substance

The blood samples were drawn at any time during the day not only for expediency but also because fasting specimens offer no particular advantage insofar as accuracy is concerned (Bruger and Somach 1932 Turner and Steiner 1939) The Bloor methods (Bloor, 1917 Bloor and Knudson 1916) for determining total cholesterol and cholesterol esters were employed throughout the study In this laboratory Miss Margaret Rourke found that they give as accurate dependable and comparable results as the Schoenheimer-Sperry technique (1934) Serum phospholipids were

TABLE VIII-1 Serum cholesterol (free esters and total) and phospholipids (lecithin*) in coronary heart disease group and matched control group each of 97 males

	CORONARY GROUP			CONTROL GROUP		
	No of cases	*Range mg %*	*Mean ± S E mg %*	*No of cases*	*Range mg %*	*Mean ± S.E mg %*
Free cholesterol	94†	37–227	110 43 ± 3 9	97	45–216	100 9 ± 3 9
Cholesterol esters	94	88–376	176 6 ± 5 5	97	70–260	141 0 ± 3 9
Total cholesterol	97	167–490	286 5 ± 6 6	97	155–455	241 9 ± 5 5
Phospholipids (lecithin)	61	177–414	316 4 ± 6 7	90	221–397	305 7 ± 4 2

*Lecithin which comprises about 80 per cent of the phospholipids is estimated by multiplying the value of the determined lipid phosphorus by a factor of 25

†Whenever the number in either group for any variable is less than 97 it shows a loss in determinations due to (*a*) laboratory wastage or (*b*) having started late in the study to determine this variable

determined by the Fiske and Subbarow technique (1925) In our determinations lecithin was expressed as 25 times the lipid phosphorus value (lipid phosphorus is the amount of phosphorus in the total lipids of the serum)

The range and the values assumed by the mean of the four serum lipids (cholesterol—free esters and total—and lipid phosphorus) in the coronary heart disease group and in the 97 matched controls are listed in Table 1 * The average serum levels of cholesterol esters and total cholesterol were greater to a highly significant degree in the coronary heart disease group than in the matched control group While the average serum levels of phospholipids and free cholesterol were higher in the coronary heart disease group as compared with the matched control group the difference did not attain significance

The distributions of the two groups for serum total cholesterol are plotted in Figure 1 The degree of overlap is apparent in spite of the significant difference in the means It is obvious that within the coronary heart disease population there were many individuals whose value of serum total cholesterol equaled that found within the healthy matched control group Furthermore the extent of the variation hardly ever exceeded one standard deviation in either

*Although the patients and controls were matched for various factors such as age weight height occupation and ethnic origin the matching did not extend to serum phospholipids and serum cholesterol (free esters and total) values Consequently in respect to these values the differences between the two groups are significant in the same way as for any unmatched groups

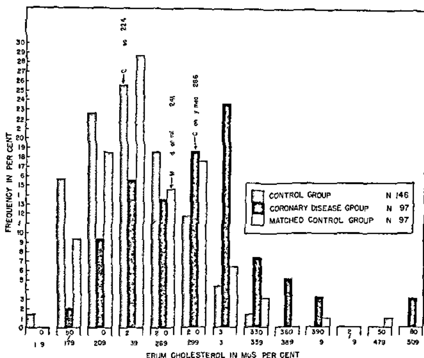


FIGURE VIII–1 Level of serum total cholesterol in coronary heart disease group unmatched control group and matched control group The distributions within the histogram are not discontinuous however there were more individuals with coronary heart disease whose cholesterol exceeded 300 mg per cent, while there were more in the control groups whose serum cholesterol was less than 210 mg per cent

direction as the following data show It was calculated that 15 per cent of the matched control group (22 individuals) exceeded the mean value of serum total cholesterol (286 mg per cent) of the coronary heart disease group However only 2 individuals in the matched control group had a serum total cholesterol greater than 352 mg per cent (the average of the coronary group plus one standard deviation) Conversely 27 members of the coronary group had a serum total cholesterol below the mean value of the matched control group (241 mg per cent) But only 2 coronary patients had a serum cholesterol below 181 mg per cent (the mean value minus one standard deviation of the matched control group)

As in the case of the serum total cholesterol there is considerable overlap of the ranges of the two groups for cholesterol esters

It was calculated from the data that 20 per cent of the matched control group (29 individuals) exceeded the mean value of serum *cholesterol esters (177 mg per cent) of the coronary group* However only 2 individuals in the matched control group exceeded the value of the mean plus one standard deviation (230 mg per cent) of the coronary group

Age Changes and Serum Cholesterol

It is generally conceded that serum total cholesterol, cholesterol esters and free cholesterol are lower in infants than in adults, however the change in these variables from infancy to maturity is a disputed subject Several studies have concluded that there is probably a rise in serum total cholesterol level after puberty in the male (Parhon and Parhon 1923a Ward 1931) while other reports have claimed that there is no such relation (Blix 1926, Foldes and Murphy 1946) Before puberty however the serum total cholesterol level seems to be lower than in adult life (Boyd 1936) and the evidence appears to support Sperry (1936) who asserts that the level is lowest during the neonatal period in (full term) infants and approximates adult levels in late prepuberty and early puberty (Sperry 1936 Offenkrantz and Karshan 1936) Page has concluded that no comparable rise exists postpuberally (Page et al 1935 Hodges et al 1943) Our calculation from his data however is not consonant with his conclusion (Gertler Garn and Bland 1950) and Keys et al (1950) have recently confirmed our results Data for ages above 65 have recently been presented (Gertler and Oppenheimer 1953)

Sampling errors technique variations and so on may account for some of the discrepancies several studies (Foldes and Murphy, 1946) were conducted on groups too small to yield results that were statistically significant Also individuals hospitalized for disorders presumably not related to cholesterol metabolism were included in some of the so called normals (Foldes and Murphy 1946) although no evidence has yet been offered that systematic errors do not appear in such procedures Furthermore the influences of race diet occupation and socio economic status though discussed in theory (Wilber and Levine 1949 Boas and Adlersberg 1945 Corcoran and Rabinowitch 1937) have not in general been considered in previous studies

TABLE VIII-2 Serum total cholesterol in coronary heart disease group of 97 males by age decades

Age	No of cases	Range mg %	Mean ± S.E mg %
20–29	7	194–400	245 0 ± 27
30–39	53	167–490	286 0 ± 9
40–49	35	208–490	301 0 ± 11
50–59	2	218–301	259

The evidence from the present study concerning the change in the level of serum total cholesterol with age is not quite clear (Tables 2 and 3) While the marked upward trend of cholesterol with age is close to significance for the coronary heart disease group the slight rise for the matched control group is certainly not significant It will be noted that the elevation of the serum total cholesterol for the coronary heart disease group over the matched control group discussed above (see also Table 1) is apparent at each age level

For the series of 146 unmatched controls the mean showed a rather marked rise from 195 mg per cent in the 20–29 year age group to 254 mg per cent in the 50–59 year age group a trend that is highly significant (Gertler Garn and Bland 1950)

If there is a rise in serum total cholesterol with age as may be suggested by these data then the clinician must consider the factor of age if he is to derive much meaning from a patient s level of serum total cholesterol In addition as will be shown below under the heading of Physique and Serum Cholesterol the factor of physique must be considered

There is some evidence that beyond the sixth decade of life no further elevation of cholesterol occurs (Keys et al 1950) there may even be a drop in cholesterol level after this time (Gertler Garn and Bland 1950 Gertler and Oppenheimer 1953) While

TABLE VIII-3 Serum total cholesterol in matched control group of 94 males by age decades

Age	No of cases	Range mg %	Mean ± S.E mg %
20–29	7	167–425	230 0 ± 12
30–39	53	155–455	227 0 ± 5
40–49	32	175–350	246 0 ± 8
50–59	2	214–270	242

No data were recorded for 3 controls in this age group

TABLE VIII–4 Serum total cholesterol levels in those of Jewish origin and of non Jewish origin in coronary heart disease group and unmatched control group

	ENTIRE GROUP		JEWS		NON JEWS	
	No of cases	*Mean age*	*No of cases*	*Cholesterol mean ± S.E mg %*	*No of cases*	*Cholesterol mean ± S.E mg %*
Coronary group	97	38 5	27	281 76 ± 14 54	70	288 75 ± 7 50
Control group	97	38 4	27	256 96 ± 12 54	70	236 67 ± 5 61

this has been interpreted by some as evidence of debility' in age it is possible that it is a statistical or selective phenomenon due to the differential mortality of low cholesterol and high cholesterol individuals Thus if elevated cholesterol is associated with de creased life span the longer lived individuals in an older group will be simply the low-cholesterol surviving population The data though scanty may point to basic factors in human survival (Dublin 1948)

Race and Serum Cholesterol

There are unconfirmed claims that atherosclerosis is practically unknown among peoples like the Chinese Eskimos and Okinawans whose diet is purported to contain very little cholesterol and whose serum total cholesterol is said to be lower than that of the American population However a survey made by the Coronary Research Laboratory did not substantiate any relation between ingested cholesterol and the level of serum total cholesterol (see Chapter X)

It is apparent that coronary heart disease occurred in our study with greater frequency in individuals who might be classified as the mid Mediterranean ethnic group We did not investigate this question completely but we did analyze the findings in two groups of individuals the Jewish and Italian Since individuals of Jewish origin were numerous in the series the levels of serum total choles terol were determined both for them and for the non Jewish popu lation of the coronary heart disease group and the matched control group The results are summarized in Table 4

In the coronary heart disease group there was a small and not statistically significant difference in the level of serum total choles terol between the Jews and non Jews In the matched control group

the difference was somewhat larger but in the opposite direction and also not statistically significant Although the cholesterol levels in the Jews of the coronary heart disease group exceeded those of the *matched control Jews the difference was not statistically significant* but between the non Jewish coronary and control groups there was a significant difference

The 6 Italians in the coronary heart disease group were compared in a similar way with the 6 Italians in the matched control group The average serum total cholesterol for those with coronary heart disease was 278 15 mg per cent while for the 6 in the matched control group it was 253 0 mg per cent In a group so small this cannot be said to be a significant difference

Lipid Indices

The ratios for total cholesterol/lipid phosphorus cholesterol esters/total cholesterol and free cholesterol/cholesterol esters are *summarized in Table 5*

It has been stated that the deposition of cholesterol and its esters does not necessarily imply the existence of hypercholesterolemia The ability of cholesterol to remain in solution in the blood requires a colloid stabilizer which will prevent its being precipitated and it has been postulated that the phospholipids act as such a stabilizer to a cholesterol suspension in vitro (Ahrens and Kunkel 1949 Thannhauser 1949) This is borne out by the fact that lecithin constituting about 80 per cent of the phospholipids is known to be antagonistic to cholesterol in certain biological and chemical *reactions and hence probably would prevent deposition* It was

TABLE VIII–5 Values of lipid indices in coronary heart disease group and matched control group

	CORONARY GROUP			CONTROL GROUP		
	No of cases	*Range mg %*	*Mean ± S E mg %*	*No of cases*	*Range mg %*	*Mean ± S E mg %*
Total cholesterol / lipid phosphorus	60*	14 5– 33 0	2? 4 ± 51	90	12 9– ?8 7	19 4 ± 33
Cholesterol esters / total cholesterol	94	36 0– 84 2	61 4 ± 1 06	97	39 0– 79 0	58 5 ± 90
Free cholesterol / cholesterol esters	94	30.3–14? 9	68 2 ± 3 09	97	36 0–133 8	76 9 ± 2 99

*A number less than 97 indicates laboratory wastage etc

suggested by Peters and Man however that it is not so much any individual lipid as the interrelation of all the lipids, their relative ratio that is important to stabilization of cholesterol An experiment reported by Ladd et al (1949) showed that rabbits fed with cholesterol and Tween 80* did not in fact, develop atherosclerosis The explanation given was that the serum phospholipids were increased to high levels and instituted a protective mechanism

Cholesterol deposition may on the other hand, sometimes result from hypercholesterolemia Popjak (1945) suggested that free cholesterol regulates the mobilization of fatty acids and the rate of phospholipid synthesis Thus it may be reasoned that an excess of free cholesterol may decrease the blood phospholipids and that this in turn may lead to deposition of cholesterol

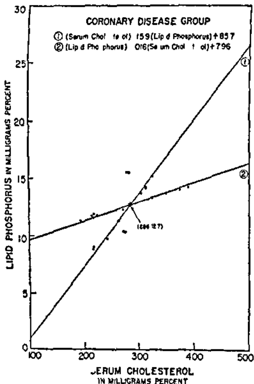
The evidence accumulated by Ladd et al (1949) Browder (1915) *Popjak (1945) and Ahrens and Kunkel (1949) are* consonant with the findings in this study on serum lipids in the healthy control group and in the coronary heart disease group There is as stated elsewhere considerable overlapping of the serum cholesterol in both groups (see Figure 1), without any indication of a threshold level of serum total cholesterol that is causally related to coronary heart disease

The coefficients of correlation between serum cholesterol and serum phospholipids were determined + 51 and + 55 *for the* coronary heart disease group and the matched control group respectively Both coefficients are highly significant demonstrating that total cholesterol and phospholipids are correlated to a high degree in both groups and strengthening the thesis that the interrelations of serum lipids are more important than either single lipid

The correlation between serum total cholesterol and lipid phosphorus is practically unaffected by eliminating by a partial correlation technique any commonality or effect that age might have on each of the two variables The scattergram depicting the relation between serum total cholesterol and lipid phosphorus for each group is given in Figure 2

The relation of total cholesterol to lipid phosphorus normally is a constant one as demonstrated by Peters and Man (1943) Formulae for calculating lipid phosphorus when serum total cholesterol is known derived from our data are

* Polyoxyethylene sorbitan mono-oleate



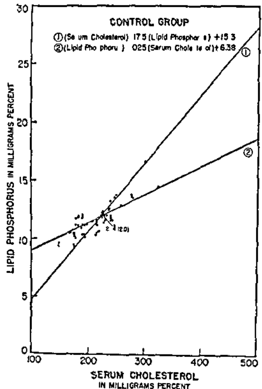


FIGURE VIII–2 Scattergrams with regression lines showing relation between serum total cholesterol and serum lipid phosphorus in coronary heart disease group and unmatched control group The coefficients of correlation between serum lipid phosphorus and serum cholesterol were + 51 ± 09 and + 66 ± 05 for the coronary group and the unmatched control group respectively

Lipid phosphorus = 0 025 total cholesterol + 6 38 (matched control group)

Lipid phosphorus = 0 016 total cholesterol + 7 96 (coronary group)

The degree of mutability of the cholesterol/lipid phosphorus ratio may be obtained from Figure 3 It is evident that an elevation or depression of either total cholesterol or lipid phosphorus or both may not necessarily produce an abnormal cholesterol/lipid phosphorus ratio The cholesterol/lipid phosphorus ratio will vary under a number of circumstances (see Table 6) It will be increased (*a*) when the serum lipid phosphorus is rising at its expected rate in the presence of serum total cholesterol that is rising faster than its expected rate (*b*) when the serum lipid phosphorus is rising slower than its expected rate *in the presence of an expected rise or a faster* than expected rise in the serum total cholesterol value

Since the time at which the writing of this report was begun several important contributions have been made to the analysis of this problem The first development came when John W Gofman made it known that giant molecules (designated S_f 10–20) are found in excessive amounts in patients with atherosclerosis and *in those who experience illnesses which are thought to be predisposing* to atherosclerosis These findings have been confirmed by several groups Additional research done by David P Barr and his associates disclosed the fact that patients who have survived coronary occlusion exhibit a reduction of albumin and alpha lipoprotein and a relative and absolute increase in beta lipoprotein While these two new findings are provocative from the evidence presented *it has not been shown that they are able to assist in pre selecting* the coronary prone individual to any greater degree than is the total cholesterol/lipid phosphorus ratio

Physique and Serum Cholesterol

Determination of the differences between the levels of the various lipids for the various dominant physiques is imperative not only *to establish the meaning of normal lipid levels* but also to determine the difference if any that exists between (*a*) the physiques within any one group and (*b*) similar physiques in any two groups Since the physical constitution is predetermined to a large degree it is reasonable to suppose, without postulating any degree of association or

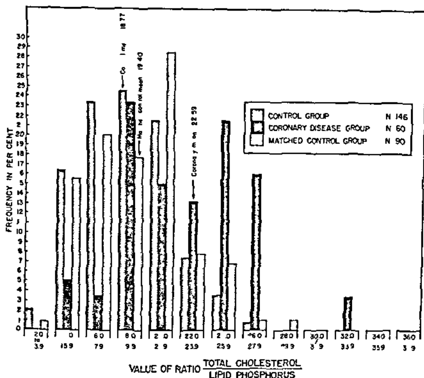


FIGURE VIII–3 Frequency distribution of total cholesterol/lipid phosphorus in coronary heart disease group unmatched control group and matched control group The mean value of the ratio was significantly greater in the coronary group than in either of the other two groups

TABLE VIII–6 Effect of various combinations of serum cholesterol and serum lipid phosphorus values on cholesterol/lipid phosphorus ratio

Serum cholesterol	*Serum lipid phosphorus*	*Chol/lipid phos ratio*
elevated	normal	elevated
elevated	elevated	need not be elevated
elevated	decreased	elevated
normal	normal	unchanged
normal	elevated	decreased
normal	decreased	elevated
decreased	normal	decreased
decreased	elevated	decreased
decreased	decreased	need not be decreased

causal relation that the chemical attributes such as serum cholesterol and serum uric acid likewise may be genetically determined Hence an attempt to associate physique with serum lipids has certain the oretical justification

This has been done in the past in studies that correlate the lipid levels with various physiques (Gildea et al , 1936 McQuarrie et al 1933 Mjassnikow 1927) The reliability of these studies is necessarily limited by their haphazard system of physique classi fication and their ill defined terminology (see Chapter IV) Some observers have used the terms obese and 'lean (Bruger and Poindexter 1934) Others presented a tripolar system with in definite poles— obese medium and lean (Labbe and Heitz 1924) Still others have followed Kretschmer s terminology (1925) but not his anthropometry with a tripolar classification of pyknic intermediate and leptosomatic (Gildea et al 1936) At best, the systems are not strictly comparable, at worst the individual varia tions in standards curtail the accuracy of the interpretations and make comparative ratings difficult However it is important to emphasize the fact that despite these drawbacks consistent and meaningful conclusions have emerged As described in Chapter IV, in order to avoid as far as possible the limitations described above without placing undue stress on ratios or index scales of build the Sheldonian system of body build rating has been selected for use in this work (Sheldon et al 1940)

The first indication that a differential relation exists between the various lipids and the physiques for both the coronary and the unmatched control groups was shown by the coefficients of correla tion which ranged from — 21 to + 23 While a few of these coefficients reached the level of significance they were so small that they did not contribute anything to our understanding of any basic trends Some of the more pertinent correlations are (*a*) between phospholipids and ponderal index (— 15 ± 13 and — 21 ± 08 for the coronary heart disease group and the control group re spectively) and (*b*) between serum total cholesterol and ponderal index (— 11 ± 10 and — 13 ± 08 for the coronary heart dis ease group and the control group respectively)

In Table 7 the values of the four lipids—free cholesterol cho-lesterol esters total cholesterol and phospholipids—are listed under physical groups which have been classified into primary domi-

TABLE VIII–7 Serum lipids by physiques in coronary heart disease group of 97 males* and unmatched control group of 146 males (Mean ± S E mg %)

Physique	No of cases	Free cholesterol	No of cases	Cholesterol esters	No of cases	Total cholesterol	No of cases	Phospho lipids†
ENDOMORPHS								
coronary	24	113 51 ± 9 4	24	176 0 ± 11 7	25	286 8 ± 12 9	19	310 6 ± 11 7
control	51	101 51 ± 4 1	51	133 1 ± 4 8	51	234 6 ± 6 6	51	311 3 ± 5 8
difference		n s		‡		‡		n s
MESOMORPHS								
coronary	43	110 2 ± 5 1	43	184 2 ± 7 0	43	294 4 ± 9 3	27	319 5 ± 10 5
control	34	104 3 ± 4 4	34	119 0 ± 4 1	34	223 3 ± 6 2	34	300 3 ± 6 0
difference		n s		‡		‡		n s
ECTOMORPHS								
coronary	9	100 4 ± 11 5	9	164 1 ± 16 4	9	264 6 ± 19 8	5	328 0 ± 12 0
control	34	96 8 ± 4 6	34	111 0 ± 4 4	34	207 8 ± 6 0	34	281 2 ± 6 4
difference		n s		§		‡		‡
MID-RANGE								
coronary	18	111 6 ± 19 0	18	165 8 ± 15 2	20	279 1 ± 16 3	11	314 0 ± 19 0
control	27	94 0 ± 5 6	27	133 4 ± 6 3	27	227 4 ± 8 2	27	298 3 ± 7 5
difference		n s		§		‡		n s
TOTAL								
coronary	94	110 4 ± 3 9	94	176 7 ± 5 5	97	286 5 ± 6 6	61	316 4 ± 6 7
control	146	99 7 ± 2 3	146	124 7 ± 2 6	146	2-4 4 ± 3 5	146	299 3 ± 3 3
difference		§		‡		‡		§

*In 3 cases free cholesterol and cholesterol esters were not determined In 36 cases lipid phosphorus (phospholipid) determinations were not made

†Phospholipids are expressed as 25 times the lipid phosphorus

‡Significant at the 1 per cent level.

§Significant at the 5 per cent level

N s —Not significant.

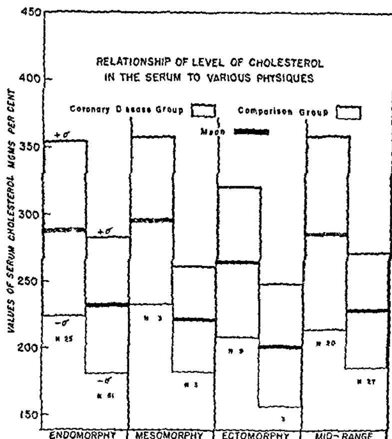


FIGURE VIII–4 Serum total cholesterol levels in coronary heart disease group and unmatched control group Within the coronary group the mesomorphs had a higher level of serum total cholesterol than the endomorphs or ectomorphs Within the control group endomorphs had a higher level of serum total choles terol than mesomorphs or ectomorphs A comparison of the coronary with the control group shows higher levels in the coronary group for all physiques the largest difference occurring in the category of mesomorphy

nances for the coronary and unmatched control groups Com parisons were also made between the means of the four major physical categories both within and between the matched control group and the coronary heart disease group (See also Figure 4)

In evaluating the relation of morphological characteristics to the level of serum total cholesterol it should be kept in mind that in an average population the levels in endomorphs, mesomorphs and mid range individuals exceed the level in the ectomorphs At the age of 35 the mean levels of serum total cholesterol for the

ectomorphs and for the other groups combined would be 207 mg per cent and 224 mg per cent respectively Abnormal levels would assume the values of 207 ± 74 mg per cent and 224 ± 82 mg per cent while high but not abnormal levels would assume values of 207 + 37 mg per cent and 224 + 41 mg per cent (Gertler Garn and Bland 1950)

The further interrelation of age and morphological characteristics with the level of serum total cholesterol is now apparent While these figures do not include enough individuals for a complete age morphological survey it is reasonable to suggest that an ectomorph at any age would possess on the average a lower level of serum cholesterol than would individuals with other physiques (see Figure 4) The assessment of age corrections and physical corrections is important before any inference is made concerning the level of a determined serum total cholesterol

Conclusions

A *coronary threshold of cholesterol does not appear to exist* if such a threshold had to be reached before coronary heart disease manifested itself the differences between physiques would be wiped out and endomorphs mesomorphs ectomorphs and mid range individuals would all conform to this threshold The fact that such a condition does not exist confirms the findings of this study namely that coronary heart disease can and does exist well below the accepted limits of hypercholesterolemia although hypercholesterolemia is undoubtedly an association of coronary heart disease among the patients as a group

If then absolute serum cholesterol values are not the answer *what explains the constantly higher lipid levels in the coronary heart* disease patients physique by physique and at the same time the continued maintenance of differences between physiques within the two groups?

The answer to both questions comes in part from an examination of the magnitude of the differences in Table 7 and Figure 4 For all lipids the differences between the coronary and unmatched control endomorphs the coronary and unmatched control ectomorphs and the coronary and unmatched control mesomorphs are of the same order of magnitude This suggests strongly the same conclusion that we have previously considered namely that in

coronary heart disease there is a specific predisposition to the disease in addition to any disturbance in lipid metabolism Since the predisposition to the disease may further augment the lipid levels many workers have decided that it is the absolute lipid level that is important However, the evidence here suggests that a high absolute lipid level is important only in that it may reveal the presence of the predisposition to coronary heart disease that is hypercholesterolemia of familial type but that with constitutionally low cholesterol levels the predisposition factor is hidden Thus coronary heart disease is found in individuals with low lipid levels because it is the predisposition constant that is important not the absolute level

The predisposition factor need not arise primarily from a difference in serum lipids but may be due to several independent additional factors One factor might be the yet unproven concept of the difference in the thickness and permeability of the coronary arteries between mesomorphs and the other physiques Thus it may be that the muscular layer of the patients with coronary heart disease (particularly the mesomorphs) is thicker thereby producing a narrower lumen which is more easily obliterated by equal amounts of plaque formation Or one may postulate the theory that between the coronary heart disease patients and the control patients there is a difference in the permeability of the coronary intimal tissue which will permit an easier penetration by the cholesterol or macrophages in the coronary intima

Cholesterol by itself is doubtless an important etiological agent in coronary heart disease but it is to be emphasized that it is only one of the links in the chain which includes such endocrine factors as the thyroid and adrenal thickening of arterial wall intima, colloidal stability, which is partially controlled by the lipid phosphorus and rates of anabolism and catabolism of cholesterol within the arterial walls Moreover vitamins such as pantothenic acid and ascorbic acid have recently been shown to influence the metabolism of cholesterol

REFERENCES

Adlersberg D Schaefer L. and Drachman S R Development of hypercholesteremia during cortisone and ACTH therapy J.A.M.A 144 909–914 1950

Ahrens E H and Kunkel H G The stabilization of serum lipid emulsions by serum phospholipids J Exper Med 90 409–424 1949

ANITSCHKOW N and CHALATOW S Über experimentelle cholesterinsteatose und ihre Bedeutung fur die Entstehung einiger pathologischer Prozesse *Centralbl f allg Path u Path Anat* 24 1–9 1913

ARKIN H and COLTON R R *An Outline of Statistical Methods* 4th Ed Barnes & Noble Inc New York 1939

BARKER N W Plasma lipoids in arteriosclerosis obliterans *Ann Int Med* 13 685–692 1939

BARR D P RUSS E M and EDER, H A Protein lipid relationships in human plasma in atherosclerosis and related conditions *Am J Med* 11 480–493 1951

BILLS C E Physiology of the sterols including vitamin D *Physiol Rev* 15 1–97 1935

BLACK H A and KAMPMEIER R H Coronary artery disease in hypothyroidism *Colorado Med* 31 262–264 1934

BLIX G Studies on diabetic lipemia *Acta Med Scandinav* 64 142–174 1926

BLOOR W R The blood lipoids in nephritis *J Biol Chem* 31 575–583 1917

BLOOR W R and KNUDSON A The separate determination of cholesterol and cholesterol esters in small amounts of blood *J Biol Chem* 27 107–112 1916

BLUMGART H L FREEDBERG A S and KURLAND G S Further experience with radioactive iodine in the treatment of euthyroid cardiac patients with angina pectoris and congestive failure *Proc New Eng Cardiovascular Soc* 1949–1950 Published by Massachusetts Heart Assn Boston 1950 Pp 47–48

BOAS E P and ADLERSBERG D Familial hypercholesterolemia (xanthomatosis) and atherosclerosis *J Mt Sinai Hosp* 12 84–86 1945

BOAS E P PARETS A D and ADLERSBERG D Hereditary disturbance of cholesterol metabolism a factor in the genesis of atherosclerosis *Am Heart J* 35(4) 611–622 1948

BOYD E M Lipid composition of blood in new born infants *Am J Dis Child* 52 1319–1324 1936

BROWDER A The effect of lecithin and cholesterol upon the division rate of paramecium *Univ California Publ Physiol 5(1) 1–3 1915*

BRUGER M The state of cholesterol and the nature of the cholesterol protein complex in pathological body fluids *J Biol Chem* 108 463–470 1935

BRUGER, M and POINDEXTER C A Relation of the plasma cholesterol to obesity and to some of the complicating degenerative diseases (diabetes mellitus essential hypertension osteo arthritis and arteriosclerosis) *Arch Int Med* 53 423–434 1934

BRUGER, M and SOMACH I The diurnal variations of the cholesterol content of the blood *J Biol Chem* 97 23–30 1932

CHEVREUL D Note sur la présence de la cholestérine dans la bile de l'homme *J de physiologie exper* 4 257–260 1824

CORCORAN A C and RABINOWITCH I M Study of blood lipoids and blood protein in Canadian eastern Arctic Eskimos *Biochem J* 31 343–348 1937

DAVIS D STERN B and LESNICK, G Lipid and cholesterol content of blood of patients with angina pectoris and arteriosclerosis *Ann Int Med* 11 354–369 1937

DENIS P S *Recherches expérimentales sur le sang humain considéré a l'état sain* C F Denis Commercy 1830

DOCK W The predilection of atherosclerosis for the coronary arteries *J.A.M.A.*, 131 875–878 1946

DUBLIN L I *Health Progress 1936 to 1945* 1st Ed Metropolitan Life Insurance Co New York 1948

DUFF G L Experimental cholesterol arteriosclerosis and its relationship to human arteriosclerosis *Arch Path* 20 81–123 259–304 1935

ELLIOT A H and NUZUM F R Cholesterol content of whole blood in patients with arterial hypertension *Arch Int Med* 57 63–72 1936

EPSTEIN A A and LANDE H Studies on blood lipoids I The relation of cholesterol and protein deficiency to basal metabolism *Arch Int Med* 30 563–577 1922

FISHER R A *The Design of Experiments* 5th Ed Oliver and Boyd Edinburgh and London 1949

FISKE C H and SUBBAROW Y Colorimetric determination of phosphorus *J Biol Chem* 66 375–400 1925

FOLDES F F and MURPHY A J Distribution of cholesterol cholesterol esters and phospholipid phosphorus in normal blood *Proc Soc Exper Biol & Med* 62 215–218 1946

GARN S M and GERTLER M M Optimum sample size and minimum significant differences in cholesterol studies in man (In preparation)

GERTLER M M GARN S M and BLAND E F Age serum cholesterol and coronary artery disease *Circulation* 2 517–522 1950

GERTLER M M and OPPENHEIMER B S The interrelationships of serum lipids in men and women past sixty years of age *Circulation* 7 533–544 1953

GILDEA E F KAHN E and MAN E B The relationship between body build and serum lipoids and a discussion of these qualities as pyknophilic and leptophilic factors in the structure of the personality *Am J Psychiat* 92 1247–1260 1936

GOFMAN J W JONES H B LINDGREN F T LYON T P ELLIOTT H A and STRISOWER B Blood lipids in human atherosclerosis *Circulation* 2 161–178 1950

GOFMAN J W LINDGREN F T ELLIOTT H A MANTZ W HEWITT J STRISOWER B and HERRING V The role of lipids and lipoproteins in atherosclerosis *Science* 111 2877 166–171 1950

HAMILTON H B and HAMILTON J B Ageing in apparently normal men I Urinary titers of ketosteroids and of alpha hydroxy and beta hydroxy ketosteroids *J Clin Endocrinol* 8 433–452 1948

HARDEGGER E RUZICKA L and TAGGMANN E Zur Kenntnis der unverseifbaren Lipoide aus arteriosklerotischen Aorten *Helvet chim acta* 26 2205–2221 1943

HEILBRON I M SIMPSON J C E and SPRING F S Structure of the sterols and bile acids *J Chem Soc* 626–635 1933 (Abstract *Chem Abstracts* 27 3 4236 1933)

HODGES R G SPERRY W M and ANDERSEN D H Serum cholesterol values for infants and children *Am J Dis Child* 65 858–867 1943

JOSLIN E P BLOOR W R and GRAY H The blood lipids in diabetes *J A M A* 69 375–378 1917

KEYS A MICKELSON O MILLER E O HAYES E R and TODD R L The concentration of cholesterol in the blood serum of normal man and its relation to age *J Clin Investigation* 29 1347–1353 1950

KRETSCHMER E *Korperbau und Charakter* 1st Ed J Springer Berlin 1921 (Tr by W J H Sprott from the 2nd German ed into English as *Physique and Character* Kegan Paul Trench Trubner London 1925)

LABBÉ, M and HEITZ J La cholesterinémie des diabetiques *Bull et mém Soc med d hôp de Paris* 48 1546–1554 1924

LADD A T KELLNER A and CORRELL J W Intravenous detergents in experimental atherosclerosis with special reference to the possible role of phospholipids *Federation Proc* Part I 8 360 1949

LANDE K E and SPERRY W M Human atherosclerosis in relation to cholesterol content of blood serum *Arch Path* 22 301–312 1936

LEARY T Crystalline ester cholesterol and atherosclerosis *Arch Path* 47 1–28 1949

LERMAN J Personal communication

LERMAN J and WHITE P D Metabolic changes in young people with coronary heart disease *J Clin Investigation* 25 914 1946

MCARTHUR C S The acetone soluble lipid of the atheromatous aorta *Biochem J* 36 559–570 1942

MCQUARRIE I BLOOR W R HUSTED C and PATTERSON H A Lipids of blood plasma in epilepsy a statistical study of single determinations in 100 epileptic and 32 normal subjects *J Clin Investigation* 12 247–254 1933

MEANS J H *The Thyroid and Its Diseases* 2nd Ed J B Lippincott Co Philadelphia 1948

MJASSNIKOW A L Beitrage zur Konstitutionsforschung Blut holesteringehalt und Konstitution *Ztschr f klin Med* 105 228–244 1927

MJASSNIKOW A L Über alimentare Beeinflussung der Cholesterinamie beim Menschen *Ztschr f klin Med* 103 767–778 1926

MORRISON L M HALL L and CHANEY A L Cholesterol metabolism blood serum cholesterol and ester levels in 200 cases of acute coronary thrombosis *Am J M Sc* 216 32–38 1948

MORRISON L M and JOHNSON K D Cholesterol content of the coronary arteries and blood in acute coronary artery thrombosis *Am Heart J* 39 31–34 1949

OFFENKRANTZ F M and KARSHAN M Serum cholesterol values for children *Am J Dis Child* 52 784–795 1936

PAGE I H KIRK E LEWIS W H JR THOMPSON W R and VAN SLYKE D D Plasma lipids of normal men at different ages *J Biol Chem* 111 613–639 1935

PAGE I H KIRK E and VAN SLYKE D D Plasma lipids in chronic hemorrhagic nephritis *J Clin Investigation* 15 101–107 1936

PARHON C J and PARHON M L hypercholestérinemie de la vieillesse *Compt rend Soc de biol* 88 231–233 1923

PETERS J P and MAN E B The interrelations of the serum lipids in normal persons *J Clin Investigation* 22 707–714 1943

PETERS J P and VAN SLYKE D D *Quantitative Clinical Chemistry* Vol I 2nd Ed Williams & Wilkins Baltimore 1946

POINDEXTER C A and BRUGER M Cholesterol content of blood in heart disease *Arch Int Med* 61 714–719 1938

POPJAK G Absorption of cholesterol from a watery suspension and its effects on plasma lipids *J Path & Bact* 57 ₄80 1945 (Abstract)

RABINOWITCH I M Arteriosclerosis in diabetes relationship between plasma cholesterol and arteriosclerosis effects of high carbohydrate–low calorie diet *Ann Int Med* 8 1436–1474 1935

REINITZER F Beitrage zur Kenntnis des Cholesterins *Monatshefte f Chemie* 9 4 1–441 1888

ROSENHEIM O and KING H The ring system of sterols and bile acids *J Soc Chem Ind* 51 464–466 193?

ROURKE M Personal communication 1949

SCHOENHEIMER R Zur Chemie der gesunden und der atherosklerotischen Aorta uber die quantitativen Verhaltnisse des Cholesterins und der Cholesterinester *Ztschr f physiol Chem* 160 61–76 1926

SCHOENHEIMER R Zur Chemie der gesunden und der atherosklerotischen Aorta *Ztschr f physiol Chem* 177 143–157 1928

SCHOENHEIMER R and SPERRY W M A micromethod for the determination of free and combined cholesterol *J Biol Chem* 106 745–760 1934

SHAPIRO S Influence of thyroidectomy splenectomy gonadectomy and supra renalectomy upon the development of experimental atherosclerosis in rabbits *J Exper Med* 45 595–607 1927

SHELDON W H STEVENS S S and TUCKER W B *The Varieties of Human Physique* 1st Ed Harper & Bros New York 1940

SNAPPER I Nutrition and nutritional diseases in the Orient *Advances Int Med* 2 577–605 1947

SNEDECOR G W *Statistical Methods* 4th Ed Iowa State College Press Ames 1946

SPERRY W M Cholesterol of the blood plasma in the neonatal period *Am J Dis Child* 51 84–90 1936

STEINER A. Significance of cholesterol in coronary atherosclero is *New York State J Med* 48 1814–1818 1948

STEINER A and KENDALL F E Atherosclerosis and arteriosclerosis in dogs fol lowing ingestion of cholesterol and thiouracil *Arch Path* 42 433–444 1946

THANNHAUSER S J *Lipidoses diseases of the cellular lipid metabolism* 1st Ed Oxford University Press New York 1940

THANNHAUSER S J Xanthomatoses Physiology of cholesterol metabolism in man *J Mt Sinai Hosp* 17 79–97 1950

TURNER K B and STEINER A Long term study of variation of serum cholesterol in man *J Clin Investigation* 18 45–49 1939

VOGEL J *The Pathological Anatomy of the Human Body* 1st Ed Lea & Blanchard Philadelphia 1847 P 531 Fig 1 Pl 10 p 534

WARD K M Study of blood cholesterol in childhood *Arch Dis Childhood* 6 329–342 1931

WIELAND H and DANE E Untersuchungen ueber die Konstitution der Gallen sauren *Ztschr f physiol Chem* 210 268–281 1932

WILBER C G and LEVINE V E Studies in physiological anthropology II The blood lipids of Alaskan Eskimos *Am J Phys Anthropol Proc* 7 285 1949

WINDAUS A Ueber den Gehalt normaler und Atheromatoser Aorten an Cholesterin und Cholesterinestern *Ztschr f physiol Chem* 67 174–176 1910

WINTERNITZ, M C THOMAS R M and LECOMPTE P M *The Biology of Arteriosclerosis* Charles C Thomas Baltimore 1938

CHAPTER IX

Biochemical Findings The Role of Serum Uric Acid

URIC acid is the principal end product of the catabolism of the purine and pyrimidine bases in man (Peters and Van Slyke 1946) Uric acid may be synthesized from the various constituents of the metabolic pool as Shemin and Rittenberg (1947) have demonstrated in that the amino acid glycine is incorporated into uric acid *The bulk of the evidence (Minkowski 1886 Schoenheimer* 1942) suggests that this synthesis takes place in the liver

Clinical Observations

The association between an abnormal uric acid metabolism and gout dates back to 1797 when Wollaston demonstrated that the deposits surrounding gouty joints are composed of uric acid to a large degree Garrod in 1848 was probably the first to suggest a causal relation between gout and an increased content of uric acid in the blood Since Garrod s observations there has accumulated a voluminous literature which confirms (Jordan and Gaston *1932 Jacobson 1938) and modifies (Schnitker and Richter 1936* Adlersberg et al 1942) his viewpoint

Hyperuricemia may exist as a result of renal failure (Brøchner Mortensen 1938) increased cellular breakdown (Isaacs 1923) or gout In reviewing many factors associated with gout one finds that it is primarily an adult male disease prepubertal and adolescent females and males are practically spared (Scudamore 1823) Bauer and Klemperer (1947) state that slightly over 95 per cent of all patients afflicted with gout are males Persons of large frame and vigorous appetite with a tendency to corpulence may be said to have a natural proclivity to gout (Roberts 1900) Scudamore reported from a study of 515 cases of gout that his youngest case was eight years old Thirteen cases appeared in the first two decades of life and the majority of his remaining cases occurred in men of

the fifth sixth and seventh decades of life These factors of male prevalence, large frame and age distribution along with familial tendency (Smyth et al 1948) are common to both coronary heart disease and the gouty diathesis (Huchard 1899)

A causal relation between the gouty diathesis and arteriosclerosis has been a clinical concept at least since the early part of this century Roberts observed clinically in patients with gout the syndrome of the runaway heart in which the palpitations were severe and necessitated rest on the part of the patient Occasionally angina pectoris and other chest pains simulating angina pectoris are associated with gout In addition Roberts stated that gouty persons exhibit a marked proclivity to the formation of such clots [thrombi causing thrombophlebitis] in the veins of the lower extremities' Similar a tute clinical observations were made by Huchard (1899) who said

> The influence of gouty diathesis on the development of arteriosclerosis and arterial atheroma has been well established and it would appear ineffectual to dwell upon this *Gout is to the arteries what rheumatism is to the heart* and this is why presence of arterial degeneration appears to a greater degree in certain families of hereditary gout Accordingly arteriosclerosis and vascular atheromata are to be found in certain subjects as the only manifestation of this diathesis Thus one sees in those of familial gout, the slow development of arteriosclerotic lesions concomitantly with joint symptoms

It was such a clinical suggestion of an association between gout and coronary heart disease that led to the study of the content of uric acid in the serum of the young coronary patient In addition, the problems were undertaken of (*a*) establishing normal values for the content of uric acid in the serum (*b*) studying the effect of differences of physique and (*c*) considering the influence of age on the serum uric acid content

The serum uric acid values for 92 men with coronary heart disease and 96 matched controls are given in Figure 1 and *Table 1* The average level of serum uric acid in the coronary heart disease group was significantly higher than that of the matched control group Forty eight per cent of the coronary patients had levels of 5 0 mg per cent or over compared with 41 per cent of the matched controls At levels of 6 0 mg per cent or over the difference was much greater 22 per cent of the coronary group as against 6 per cent of the matched controls The interpretation of the higher levels

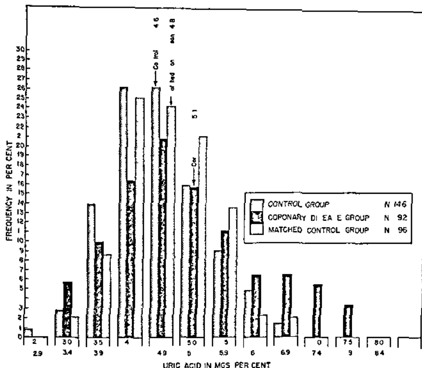


FIGURE IX–1 Frequency distribution of uric acid in coronary heart disease group unmatched control group and matched control group It is to be noted that 22 per cent of the individuals within the coronary group had serum uric acid values greater than 6 0 mg per cent while only 6 per cent of the unmatched or matched control groups had serum uric acid values greater than 6 0 mg per cent

TABLE IX–1 Serum uric acid levels* in coronary heart disease group of 92 males† and matched control group of 96 males†

Level mg %	*Coronary group*	*Cont ol g oup*
	No	*No*
3 0–3 4	5	[illegible]
3 5–3 9	9	8
4 0–4 4	15	24
4 5–4 9	19	23
5 0–5 4	14	20
5 5–5 9	10	13
6 0–6 4	6	4
6 5–6 9	6	2
7 0–7 4	5	0
7 5–7 9	3	0
	Level mg %	*Level mg %*
Range	3 0–7 8	3 1–6 9
Mean ± S E.	5 13 ± 1.	4 85 ± 07

Normal range of serum uric acid is 2.0–5 0 mg. per cent.
†Several values were not obtained owing to sampling errors or l boratory wastage etc.

in the coronary group will be discussed in the sections that follow

Both the coronary heart disease group and the matched control group were subdivided by age, and the average serum uric acid levels were calculated It was obvious that there was no change of serum uric acid with age This contrasts with the change in serum total cholesterol which showed a small but significant rise with age in both groups

The CUP Index

It is evident from the discussion in Chapter VIII that there are factors other than the level of serum cholesterol responsible for the deposition of cholesterol in the intima The colloidal stability the quantity and quality of the surface active agents and the intimal permeability may play a role in the extent to which cholesterol is deposited in the intima It has been shown (Chapter VIII) that the ratio of serum total cholesterol to lipid phosphorus is probably more important than the level of either component Lecithin (80 per cent of serum phospholipids) may act like a cationic surface active agent Uric acid in its lactam state contains three free hydroxyl ions and theoretically could act as an anionic surface active agent

Because of the possibility that the phospholipids and uric acid may oppose each other as surface active agents and because of the theoretical possibility that actual removal of cholesterol to the intima may be brought about by the force of the entire combination of surface active agents (of which lecithin and uric acid are only two) it was decided to combine the uric acid value with the total cholesterol/lipid phosphorus ratio Thus if K represents the CUP index or numerical value of this total relation

$$K = \text{serum uric acid mg per cent} \times \frac{\text{serum total cholesterol mg per cent}}{\text{serum lipid phosphorus mg per cent}}$$

The additional abnormal factor of serum uric acid may prove to have some enhancing effect on the deposition of serum cholesterol in the intimal tissue by alteration of the permeability as do some of the surface active agents

In Figure 2 and Table 2 are given the CUP indices for the matched control group and coronary heart disease group It will be shown that a consideration of all three variables known to be

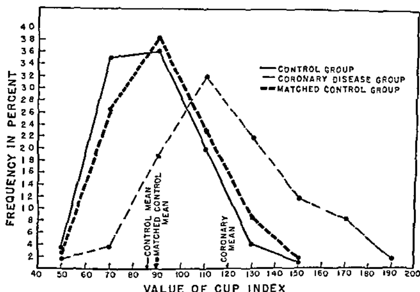


FIGURE IX–2 Frequency distribution of CUP index in coronary heart disease group of 59 unmatched control group of 146 and matched control group of 83 The polygons of the two control groups are practically identical while the polygon of the coronary group shows signs of distinct separation at the higher levels

TABLE IX–2 CUP index* in coronary heart disease group of 59† males and matched control group of 83‡ males

Index level	*Coronary g oup*	*Co t ol g o p*
	No	*No*
40–59	1	2
60–79	[illegible]	2[illegible]
80–99	11	32
100–119	19	19
120–139	13	7
140–159	7	1
160–179	5	0
180–199	1	0
	Index level	*Index level*
Range	49–188	58–151
Mean ± S E	119 ± 4	9[illegible] ± 2
	% below 119	*% below 119*
	50 0§	90 4§

*Serum total cholesterol mg % / serum l p d phosphorus mg × serum uric acid mg. %

†For 38 patients e ther uric acid or l pid phosphorus was not determ ned

‡For 14 controls either ur acid or l p d phosphorus was not determi ed.

§At least 50 per cent are always below the me n

associated with coronary heart disease is more meaningful than any one variable considered individually

The mean CUP index of the coronary heart disease group was significantly higher than that of the matched control group It is interesting that 90 4 per cent of the matched control group were below the mean value of the coronary heart disease group Of the 83 matched controls only 1 exceeded 147 which represents the value of one standard deviation above 119 (the mean of the coronary heart disease group)

The CUP index was also determined for the larger group of unmatched controls The distribution of the index was essentially similar to that of the matched control group, the mean was 87 (see Figure 2)

Uric Acid and Morphological Characteristics

Since it had been shown that the highest levels of serum total cholesterol occur in the mesomorphs who experience coronary heart disease it was decided to study the relations between serum uric acid and morphological characteristics in both the matched control and coronary groups Consequently coefficients of correlation were determined between serum uric acid and height weight and ponderal index

Certain information may be gathered from the coefficients of correlation (Table 3) (*a*) there were insignificant correlations between uric acid and height in the coronary heart disease group and the matched control group (*b*) although the positive correlations between weight and uric acid were fairly small they did attain statistical significance for both groups (*c*) there were small but significant negative correlations between ponderal index and uric acid in both groups

TABLE IX–3 Uric acid coefficients of correlation in coronary heart disease group and matched control group each of 92 males*

Correlation with serum uric acid	*Coronary group*	*Control group*
Height	+ 10 ± 10	+ 05 ± 10
Weight	+ 23 ± 10	+ 26 ± 10†
Ponderal index	— .22 ± 10	— 25 ± 10†

Owing to sampling errors laboratory wastage etc 5 samples were not obtained
†Difference is significant.

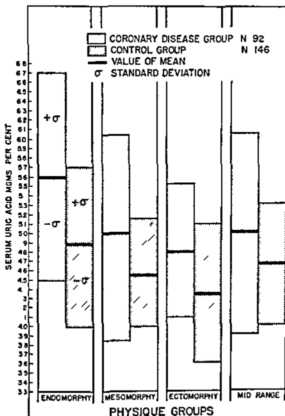


FIGURE IX–3 Serum uric acid levels by physiques in coronary heart disease group and unmatched control group A comparison of the physiques within the coronary and unmatched control groups shows that in both the endomorphs had a higher level of serum uric acid than ectomorphs A comparison of the coronary group with the unmatched control group shows higher levels in the coronary group for all physiques the largest difference occurring in the category of endomorphy

Thus linear measurement per se is unrelated to serum uric acid but as the weight and body mass of the individual increase as reflected by the ponderal index the serum uric acid has a tendency to be elevated Such rough estimates of physique suggested that dominant ectomorphs would have lower levels of uric acid in the serum while dominant mesomorphs and endomorphs would have higher levels of serum uric acid To evaluate these suggestions more critically correlations were made (see Figure 3) between the Sheldonian classifications (endomorphy mesomorphy and ecto

TABLE IX–4 Serum uric acid by physiques in coronary heart disease group of 92 males* and unmatched control group of 146 males

Physique	No of cases	SERUM URIC ACID MG % Range	Mean ± S.E
ENDOMORPHS			
Coronary	23	3 6–7 6	5 61 ± 23
Control	51	3 1–6 9	4 87 ± 12
difference			†
MESOMORPHS			
Coronary	41	3 2–7 7	4 98 ± 18
Control	34	3 6–5 4	4 59 ± 09
difference			n s
ECTOMORPHS			
Coronary	9	3 9–6 1	4 80 ± 23
Control	34	2 9–5 8	4 34 ± 12
difference			n.s
MID RANGE			
Coronary	19	3 2–7 8	5 01 ± 27
Control	27	3 8–6 2	4 65 ± 12
difference			n s

*In 5 cases serum uric acid was not determined owing to sampling errors and laboratory wastage etc
†Highly significant.
N s —Not significant

morphy) and serum uric acid It was thought that these correlations would be more meaningful than the correlations between height weight and ponderal index because the actual make up of the body mass could be defined more accurately (see Table 4 and Figure 3)

Several striking features in the distribution of serum uric acid among the physiques of both the coronary heart disease group and the unmatched control group are these (*a*) endomorphs possessed the highest level of serum uric acid (*b*) ectomorphs possessed the lowest level of serum uric acid (*c*) this contrast was statistically significant The only other contrast between body types which was significant was within the coronary heart disease group where the endomorphs differed statistically from both the mesomorphs and the ectomorphs

The only comparison between the coronary heart disease group and the control group which was significant was that for the endomorphs From such observations it is reasonable to suggest that hyperuricemia endomorphy and coronary heart disease are interrelated in some as yet unexplained manner

Conclusions

The presence of an elevated serum uric acid in coronary heart disease in the absence of renal damage or any other conventional cause such as excessive protein catabolism poses an interesting question Is the excessive uric acid in the serum due to a positive uric acid balance with an excessive endogenous production as the dominant factor? Is this mechanism a genetic phenomenon? There is evidence that hyperuricemia is due to an autosomal dominant gene but only a portion of the heterozygotes develop gout (Smyth et al 1948)

The uric acid–endomorphic relation permits further insight into the relative importance of endomorphy or fatty tissue in coronary heart disease It has been shown that the coronary physique is mesomorphic (muscular) with endomorphy (softness roundness) as a secondary characteristic It was also shown that the level of total cholesterol in the serum is on the average higher in coronary heart disease and that this higher level appears greatest in the mesomorphic group The uric acid studies in the coronary heart disease group revealed that serum uric acid is highest in the dominant endomorphs Thus it may be possible to relate the mesomorphic component in coronary heart disease to the maximal levels of serum cholesterol and the endomorphic component to maximal levels of serum uric acid

The significant difference of the mean levels of serum uric acid between those of the same body build in the matched control group and the coronary heart disease group indicates that additional factors other than body build are contributing to this difference the cause of which is unknown at present

What harmful effects on the intima may be attributed to hyperuricemia? Does uric acid act as an intimal conditioning agent (surface active agent) which is conducive to cholesterol deposition especially if there is an instability in the colloidal state of the serum lipids? These problems have not been adequately studied and cannot be discussed at this time

The CUP index may or may not prove to be especially useful in pre selecting those who are prone to coronary heart disease It does separate the normal group from the coronary heart disease group more effectively than any other index we have at the present time

REFFRENCES

ADLERSBERG D GRISHMAN E and SOBOTKA H Uric acid partition in gout and in hepatic disease *Arch Int Med* 70 101–120 1942

BARNES F W and SCHOENHEIMER R On the biological synthesis of purines and pyrimidines *J Biol Chem* 151 123–139 1943

BAUER W and KLEMPERER F Gout in *Diseases of Metabolism* Ed by G G Duncan 2nd Ed W B Saunders Philadelphia 1947

BRØCHNER MORTENSEN K Uric acid in blood and urine in Bright s disease *Acta Med Scandinav* 96 438–461 1938

GARROD A B Observations on certain pathological conditions of the blood and urine in gout rheumatism and Bright s disease *Medico Chir Tr London* 31 83–97 1848

GERTLER M M GARN S M and LEVINE S A Serum uric acid in relation to age and physique in health and in coronary heart di ease *Ann Int Med* 34 1421–1431 1951

HUCHARD H *Traité clinique des maladies du coeur et de l aorta* 3rd Ed O Doin Paris 1899–1903 3 vols

ISAACS R Pathologic physiology of polycythemia vera *Arch Int Med* 31 289–296 1923

JACOBSON B M The uric acid in the serum of gouty and of non gouty individuals its determination by Folin s recent method and its significance in the diagnosis of gout *Ann Int Med* 11 1277–1295 1938

JORDAN E P and GASTON D The blood uric acid in disease *J Clin Investiga tion* 11 747–752 1932

MINKOWSKI O Ueber den Einfluss der Leberexstirpation auf den Stoffwechsel *Arch f exper Path u Pharmakol* 21 41–87 1886

PETERS J P and VAN SLYKE D D *Quantitative Clinical Chemistry* Vol I 2nd Ed Williams and Wilkins Co Baltimore 1946

ROBERTS W Gout in *A System of Medicine by Many Writers* ed by T C Allbutt and H D Rolleston Macmillan London 1905–1911 Vol 3 pp 155–195

SHEMIN D and RITTENBERG D On the utilization of glycine for uric acid syn thesis in man *J Biol Chem* 167 875–876 1947

SCHNITKER, M A and RICHTER A B Nephritis in gout *Am J M Sc* 192 241–252 1936

SCHOENHEIMER R *The Dynamic State of Body Constituents* Harvard University Press Cambridge Mass 1942

SCUDAMORE C *A Treatise on the Nature and Cure of Gout* 4th Ed Longman Hurst Rees Orme and Brown London 1823

SMYTH C J COTTERMAN C W and FREYBERG R H The genetics of gout and hyperuricemia—an analysis of nineteen families *J Clin Investigation* 27 749–759 1948

WOLLASTON W H On gouty and urinary concretions *Phil Tr Royal Soc* 87 386–400 1797

CHAPTER X

Diet Cholesterol Ingestion and Atherosclerosis

DIETARY factors have been implicated in the pathogenesis of athero sclerosis A general relation of the disease to nutrition has been claimed on the grounds that atherosclerosis is more frequent in individuals who are overweight (Wilens 1947) and that it is decreased in the population during periods of famine (Aschoff 1924 Keys 1953) Whether there is a causal relation between atherosclerosis and nutrition however is open to considerable question The relation of weight to coronary heart disease has already been discussed in Chapter IV where it was shown that in the present study the patients were actually not overweight as compared with the controls And as far as malnutrition is concerned (see below under Studies by Other Investigators) the presence of many variables makes it uncertain whether this condition leads to death from atherosclerosis there is e g the fact that suscepti bility to other diseases is lowered by poor nutrition with the result that fewer undernourished people live to the age at which degenera tive disease sets in

A major topic of investigation in this study was the relation of cholesterol ingestion to atherosclerosis Claims have been made that atherosclerosis is less frequent in countries where cholesterol is ingested in small quantitie than in those where amounts of cho lesterol ingested are greater (Dock 1946 Snapper 1947) These specific questions will be discussed later in the chapter

Source of Cholesterol in Atherosclerosis

It is well known that serum total cholesterol is frequently ele vated in coronary heart disease It is also well known that athero sclerotic plaques which are responsible for coronary heart disease contain cholesterol and cholesterol esters to a greater degree than does the surrounding arterial tissue These two known facts are

thought by many observers to be causally related They reason that (*a*) where cholesterol is ingested in large quantities it produces an elevated serum cholesterol, and (*b*) an elevated serum cholesterol will eventually produce atherosclerosis Chapter VIII has reviewed two aspects of evidence that opposes these contentions (*a*) the serum cholesterol distribution curves of both the control group and the coronary heart disease group overlap to a considerable degree and (*b*) the interrelations of the other lipids such as phospholipids are as important in the deposition of cholesterol as cholesterol itself Furthermore, no one has demonstrated satisfactorily in human beings the source of the cholesterol in the atherosclerotic plaques Does it come from the cholesterol that exists in the serum? If so is the source mainly exogenous or endogenous? Does cholesterol arise from the degenerating intimal cells? Is it synthesized by the intimal tissue in sufficient quantities to produce atheromatous plaques? Is it brought to the plaques by the Kuppfer cells or by some other means? These questions were considered in the course of the present project

Relation of ingested cholesterol to serum cholesterol

DIET RECORD In order to obtain data on which to base our consideration of these questions a diet history was compiled for 90 males with coronary heart disease and for an unmatched control group of 139 healthy males * covering the period at least 10 years prior to their myocardial infarction Information designed to reveal intake of cholesterol and uric acid stressed not only the foods that obviously contain cholesterol and uric acid but also those that contain the greatest percentage of amino acids which are thought to be cholesterol precursors (Duncan 1947) Accordingly, the diet record was adequate so far as protein and fat intake is concerned

The total daily fat and protein intake calculated from the diet cards (see Appendix D) is recorded in Table 1 The difference between the means of the two groups is significant The information however does not indicate the total caloric intake of either group which should also include calories supplied in the form of carbo

*All data in this chapter are based on these numbers of patients and unmatched controls In each group records were lacking for 7 men

TABLE X–1 Fat and proteins ingested by coronary heart disease group of 90 males and unmatched control group of 139 males

	CORONARY GROUP		CONTROL GROUP	
	Mean daily intake gm	*Calories*	*Mean daily intake gm*	*Calories*
Fats	66	594	90*	810
Proteins	52	208	62*	248

*Difference is significant.

hydrates consequently it is not known whether the coronary heart disease group had a greater or lesser caloric intake than the control group Although the diet record thus affords an inadequate assessment of carbohydrate intake it may be reasonably assumed that the total amounts of carbohydrates were proportionate to those of fats and proteins and hence like them were not excessive in either group

FINDINGS BASED ON DIET RECORD Because of the claims that increased ingestion of cholesterol will produce an elevated level of serum cholesterol it was decided (*a*) to determine the average amount of cholesterol ingested per week for both the coronary heart disease group prior to infarction and the control group and (*b*) to correlate the amount of cholesterol ingested with the level of cholesterol in the serum for these two groups The results are summarized in Tables 2 and 3

The control group on the average ingested significantly more cholesterol than the coronary heart disease group (18 per cent more) but had significantly less cholesterol in the serum than the coronary group (224 4 mg per cent as against 286 5 mg per cent see Chapter VIII Table 7)

TABLE X–2 Mean cholesterol intake in coronary heart disease group of 90 males and unmatched control group of 139 males

		GM PER WEEK	
	No of cases	*Range*	*Mean ± S.E*
Coronary group	90	6–66	3.3 ± 15
Control group	139	6–94	39 ± 1.

Significantly greater

TABLE X–3 Ingested amounts and serum levels of cholesterol for 10 individuals with highest and 10 with lowest cholesterol ingestion in coronary heart disease group and unmatched control group

	Coronary patients mean ± S E	Controls mean ± S.E
10 WITH HIGHEST CHOLESTEROL INGESTION		
ingested amount (gm per week)	5 67 ± 15	6 98 ± 31
serum total cholesterol (mg %)	288 ± 21 9	213 ± 11 4
10 WITH LOWEST CHOLESTEROL INGESTION		
ingested amount (gm per week)	1 34 ± 10	1 37 ± 13
serum total cholesterol (mg %)	271 ± 14 2	222 ± 15 6

As a further check on the degree of correlation between cholesterol ingestion and serum cholesterol it was decided to determine the level of serum cholesterol in those who ingested the most and the least cholesterol in both coronary and control groups The results are summarized in Table 3

It is clear that in the coronary heart disease group in spite of the lower average *ingestion* of cholesterol, both the individuals who ingested large quantities and those who took small quantities have an average *serum* total cholesterol significantly higher than that of the control group Furthermore the level of serum total cholesterol within the coronary group does not change appreciably with these large differences in cholesterol ingestion

*From these results it is apparent that a factor or factors in addi*tion to ingested cholesterol is important This conclusion gains further support from the small and not significant coefficients of correlation between the amount of ingested cholesterol and the level of serum cholesterol for both groups + 05 for the unmatched control group and — 09 for the coronary heart disease group The lack of correlation is well shown in Figure 1 There is thus practically no correlation between the amount of cholesterol ingested and the level of cholesterol in the serum

This fact, in combination with the finding that serum cholesterol was higher in the coronary than in the control group suggests that a major source of cholesterol could possibly be endogenous This viewpoint is currently espoused by Gould (1951) and Bloch (1954) Bloch s work with labeled acetate and squalene has given much information on steroid biogenesis

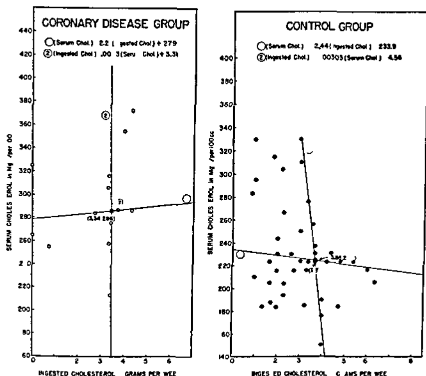


FIGURE X–1 Scattergrams with regression lines showing relation of ingested total cholesterol to serum total cholesterol in coronary heart disease group of 90 males and unmatched control group of 139 males The coefficients of correlation were not significant being — 09 ± 08 and + 05 ± 11 for the coronary group and the control group respectively

FINDINGS BASED ON TEST MEALS The relation of ingested cholesterol to serum cholesterol was studied not only by means of the diet record, but by test meals No attempt was made to solve all the numerous problems that may arise from variations of diet, but the tests were designed to determine the effects on the levels of serum total cholesterol and cholesterol esters of coronary patients that will be produced by

Test 1 *Fat* ingestion of 25 gm of butter and 3 slices of white toast with a cup of plain tea

Test 2 *Fat and cholesterol* ingestion of 25 gm of butter and 5 gm of cholesterol in the form of egg yolk

Test 3 *Cholesterol* ingestion of 5 gm of cholesterol in the form of egg yolk mixed as an eggnog

Test 4 *Low cholesterol diet* over a period of 6 to 30 months

In all tests determinations were made of changes in serum total cholesterol cholesterol esters, and cholesterol esters/total cholesterol ratio

The first three tests were performed on coronary patient No 049 On successive days his total cholesterol and cholesterol esters were determined after an all night fast then he was given a test meal on the first day at 11 A M on the second and third at 9 A M The results given in Tables 4 5 and 6 show that in Tests 1 and 3 the levels and ratios of serum total cholesterol and cholesterol esters were practically unaffected by the test procedures whereas in Test 2 they were increased to a slight degree

The conclusions derived from these three experiments are consonant with the observation that ingested cholesterol in physiological amounts will best be absorbed when absorbable fats (usually unsaturated fatty acids) are present in quantitative relations Similar observations have been made by Steiner and Domanski (1941) and Cook (1936 1937)

Test 4 conducted on coronary patient No 052 indicated that when the ingested cholesterol is restricted to approximately 150 mg daily there is a rapid decline in the level of serum total cholesterol and serum cholesterol esters which reach their minimal level in about 10 to 18 days (see Figure 2) This minimal level is usually from 25 to 40 per cent lower than the original cholesterol level and 30 to 50 per cent lower than its original esterified component However the levels do not remain stationary in spite of a continued low

TABLE X–4 Serum cholesterol levels after Test 1

	Fast ng before 11 00 A M *meal*	*1? 45* P M	*2 45* P M	*4 45* P M	*6 45* P M
Total cholesterol (mg %)	630	585	537	489	489
Cholesterol esters (mg %)	354	345	270	—	—
Cholesterol esters / Total cholesterol	56	58	50	—	—

TABLE X–5 Serum cholesterol levels after Test 2

	Fasting before 9·00 A.M *meal*	*10 0* A.M.	*1? 20* P M	*2 0* P M	*4 30* P M
Total cholesterol (mg %)	693	708	729	663	651
Cholesterol esters (mg %)	347	342	367	375	412
Cholesterol esters / Total cholesterol	*50*	*48*	*50*	*56*	*63*

TABLE X–6 Serum cholesterol levels after Test 3

	Fa t g b fo e 9·00 A M *meal*	*11 45* A.M	*2 10* P M	*5 10* P M
Total cholesterol (mg)	577	537	537	531
Cholesterol esters (mg %)	399	336	347	366
Cholesterol esters / Total cholesterol	69	63	65	68

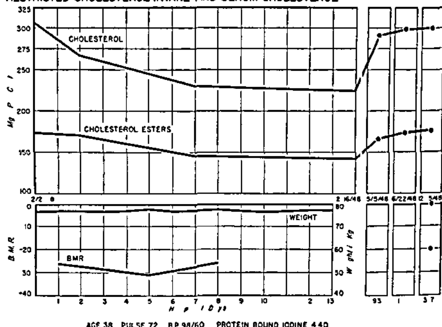


FIGURE X–2 Record of patient hospitalized for a period of 2 weeks and then followed very closely for 10 months at home While in the hospital the patient was placed on a low cholesterol diet which was continued for 10 months The serum total cholesterol fell from 310 mg per cent to 235 mg per cent in 7 days and remained at that level for approximately a month Thereafter the cholesterol rose steadily reached its former level within 4 1/2 months and remained at that level

cholesterol diet and when the patient is studied for longer periods a slow rise in total cholesterol and cholesterol esters is observed The levels attain their original values in 7 to 12 months and then remain high

Thus it may be concluded that the effect of a low cholesterol diet is to produce an immediate lowering of serum total cholesterol and esterified cholesterol But this trend ceases within a fortnight and even if the diet is continued the tendency reverses itself and the levels of total cholesterol and esterified cholesterol rise slowly and reach their original values within a year

One might presume that the original lowering of cholesterol is due to restriction of the exogenous source However since serum cholesterol is derived from both exogenous and endogenous sources it is probable that when the former source is removed the latter

becomes more active and eventually restores the equilibrium It is noteworthy that there was no significant fluctuation in weight during the course of these experiments

Similar observations were made on 6 other coronary heart disease patients and in each case the pattern was the same (See Figure 3 for a summary of these 6 cases) On the basis of this evidence one may seriously question the merits of a low cholesterol diet and its role in lowering the serum cholesterol However since the relation between an elevated serum cholesterol and atherosclerosis is not entirely clear one must reserve judgment on the capacity of the low cholesterol diet to prevent the disease The ingestion of lipids may play a role in cholesterol deposition as suggested by Moreton (1948) Walker (1953) summarized the effects of dietary restriction on serum lipids and has demonstrated that weight reduction reduces serum lipids

INGESTION OF CHOLESTEROL PRECURSORS Schoenheimer and his school have demonstrated by the use of deuterium labeled precursors that cholesterol may be synthesized in the mouse (Schoenheimer and Breusch 1933) Furthermore it has been shown that

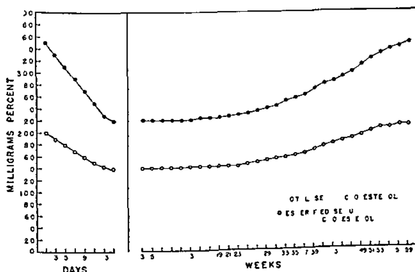


FIGURE X-3 Effect of prolonged restriction of dietary cholesterol summary of data on 6 patients After a transient drop the level of serum total cholesterol gradually increased (presumably by endogenous means) to its former point and remained there while the patients were on the low cholesterol diet

cholesterol is synthesized from amino acids such as leucine and alanine from acetic acid, and from fatty acids such as myristic and butyric acids (Duncan, 1947, Rittenberg and Bloch 1945 Ponticorvo et al 1949) In all probability similar mechanisms of synthesis exist in man, despite the failure to demonstrate all of them as yet In our study analysis of the diet records revealed no correlation between the amounts of these substances in the diet and the level of serum cholesterol

Relation of serum cholesterol to atherosclerosis

The phospholipids in a manner as yet unknown, may act as a colloidal stabilizer by maintaining the serum cholesterol in suspension and preventing its tendency to be attracted to the intimal tissue and thus to be deposited there (see Chapter VIII Ladd et al) Moreton (1948) brought out an interesting theory supported by experimental evidence, of the etiology of atherosclerosis He demonstrated that fat particles (chylomicrons) appearing in normal plasma during alimentary hyperlipemia are of colloidal size and upon ultracentrifugation, are shown to consist of mainly neutral fats and lipid phosphorus in addition to minute quantities of cholesterol and other substances (Gofman 1950) Moreton suggests that the cumulative effect of fatty meals over a lifetime by producing transient showers of large lipid particles in the plasma is the underlying cause of atherosclerosis in normal human beings Following this observation Becker and his associates (1949) showed that hyperchylomicronemia occurs at any age following fat containing meals However the intensity size, and duration of the chylomicron state increases with the age of the individual The abnormal postabsorptive chylomicron state in older human beings is restored to the normal state by the use of detergents and lipases

These three separate observations by Ladd and his co workers (see Chapter VIII) by Moreton and by Becker and his associates are interrelated and suggest that a disturbance in the colloidal state of the blood may be one of the most important factors in atherosclerosis These aforementioned studies support our observation that cholesterol is not the only factor involved in atherosclerosis (Gertler and Garn 1950) In addition they demonstrate the necessity of increasing the rapidity of lipid absorption and utilization in older individuals The Moreton hypothesis still does not clarify the ques

tion of cholesterol ingestion and its relation to atherosclerosis It does not explain the mechanism of atherosclerogenesis particularly when there is practically no cholesterol available in the hyperchylo micronemic state

Gofman and his co workers (1950) have shown that the blood of individuals with atherosclerosis contains an increased concentra tion of large cholesterol molecules of the class S_f 10–20 By the use of a low fat low cholesterol diet the concentration of this large molecule S_f 10–20 was decreased to normal values On this basis Gofman recommends the use of a low cholesterol low fat diet Further study of this moot point is in progress by various groups of investigators (see Walker 1953)

General Relation of Cholesterol Ingestion to Atherosclerosis

Diet in other countries

A possible association between a low incidence of atherosclerosis and a low ingestion of cholesterol has been suggested by various reports stating that atherosclerosis in the Chinese and Okinawans is uncommon presumably because of a diet which is normally low in cholesterol However there is no conclusive evidence that the incidence of either atherosclerosis or coronary heart disease is lower in China than elsewhere Hospital records in China are not so well kept as they are in the United States and local territorial and national death records are not so accurate there as in this country Even if they were extensive corrections of the statistical data would be required before the interpretations could be considered valid For example there is a smaller percentage of the Chinese than of the American population falling into the age groups in which athero sclerosis is common because of the high rate of infant mortality and the high death rates from other causes such as tuberculosis and other infectious diseases in China (Snapper 1947) Consequently a confirmed lower death rate from atherosclerosis in China might reflect merely the fact that the age distribution is lower

Similarly the purported low incidence of coronary heart disease or atherosclerosis in Okinawans has been considered to be causally related to the diet which is said to contain little or no cholesterol In reviewing P E Steiner s material on autopsies performed on 150 Okinawans (51 males and 99 females) from 1 to 100 years of age it is evident that 7 individuals (6 males over 55 years and 1 female

of 91) had visible aortic atherosclerosis (P E Steiner 1946) Thus 6 males out of 51 who were examined (12 per cent) showed atherosclerosis In another series of autopsies performed on about 200 Okinawans during World War II the incidence of athero sclerosis in both men and women almost approximated that observed in the United States (Zimmerman 1954)

Studies by other investigators

Further support of the dietary causation of atherosclerosis is offered by those who quote as evidence (*a*) the decrease in athero sclerosis in Germany immediately following World War I (Aschoff 1924) (*b*) the lower incidence of atherosclerosis in chronic alco holics (Wilens 1947) and (*c*) the decrease of atherosclerosis in ill nourished and lean individuals (Wilens 1947) The common denominator in all three categories appears to be a low fat intake due to dietary restriction Critical examination of the data reveals that the authors claims are based upon the assumption that in these groups the fat and hence the cholesterol intake is decreased thereby decreasing the propensity of the individual to develop atherosclero sis There is no further evidence however to support these assump tions Actually ill nourished individuals and chronic alcoholics are more prone to other diseases at an early age and hence do not always attain the age at which degenerative diseases manifest themselves However much more complete world wide study is needed

Other evidence for a relation between cholesterol ingestion and atherosclerosis is based on experiment There are data to indicate that excessive cholesterol feedings may produce atherosclerosis in the rabbit (Anitschkow and Chalatow 1913) or dog (Steiner and Kendall 1946) Such evidence has been accepted as applicable to man by some observers (Leary 1949) Others are reluctant to make this acceptance because (*a*) the amount of cholesterol em ployed in these experiments far exceeds the highest physiological level of ingestion by man and (*b*) the lesions are distributed mainly in the distal arteries and to a lesser degree involve the coronary arteries Duff (1935) has questioned whether the disease process in man and in rabbits is comparable

Summary

It has been claimed from evidence based on (*a*) animal ex periments (*b*) statistical studies in various sections of the world

and (*c*) human studies that dietary intake particularly low choles terol diet, influences atherosclerogenesis However in a critical analysis of the data it is observed that the statistics on the reportedly low incidence of atherosclerosis in countries such as China are probably distorted greatly The animal feeding experiments reveal an increased incidence of atherosclerosis in those animals which are fed cholesterol in large quantities These experiments however may or may not be applicable to man In man it has been shown that the amount of cholesterol ingested has little bearing on the level of serum cholesterol Although it has been demonstrated that an association exists between the level of *serum* lipids and clinical atherosclerosis there are no studies available which demonstrate a causal relation between *ingested* lipids including cholesterol and atherosclerosis either from a clinical viewpoint or a pathologic viewpoint There may however be other dietary factors such as ingestion of fat or of cholesterol precursors which do relate to atherosclerosis The whole question of dietary relation to athero sclerosis still remains an area for investigation for there is good supportive evidence on both sides

REFERENCES

AHRENS E. H and KUNKEL, H G The stabilization of serum lipid emulsion by serum phospholipids *J Exper Med* 90 409–424 1949

ANITSCHKOW N and CHALATOW S Über experimentelle cholesterinsteatose und ihre Bedeutung fur die Entstehung einiger pathologischer Prozesse *Centralbl f allg Path u Path Anat* 24 1–9 1913

ASCHOFF L. *Lectures in Pathology* P B Hoeber New York, 1924

BECKER G H MEYER, J., and NECHELES H Fat absorption and atherosclerosis *Science* 110 529–530 1949

BLOCH K. Biological synthesis of cholesterol *Harvey Lectures* Academic Press New York, 1954 Pp 68–88

BLOCH K BOREK, E. and RITTENBERG D Synthesis of cholesterol in surviving liver *J Biol Chem* 162 441–449 1946

COOK R P Cholesterol feeding and fat metabolism. *Biochem J* 30 1630–1636 1936

COOK, R P Fat feeding and cholesterol absorption *Biochem J* 31 410–415 1937

Diseases of Metabolism Detailed Methods of Diagnosis and Treatment A Text for the Practitioner ed by G G Duncan (with contributions by Walter Bauer and others) 2nd Ed W B Saunders Philadelphia, 1947

DOCK, W The predilection of atherosclerosis for the coronary arteries *J A M A* 131 875–878 1946

DUFF G L. Experimental cholesterol arteriosclerosis and its relationship to human arteriosclerosis. *Arch Path* 20 81–123 259–304 1935

GERTLER, M M., and GARN S M The lipid interrelationship in health and in coronary artery disease *Science* 11° 14–16 1950

GOFMAN J W LINDGREN F T ELLIOTT H A MANTZ W HEWITT J STRISOWER B and HERRING V The role of lipids and lipoproteins in atherosclerosis *Science* 111 2877 166–171 1950

GOULD R G Lipid metabolism and atherosclerosis *Am J Med* 11 209–227 1951

J A M A editorial Arteriosclerosis 141 392 1949

KEYS A Personal communication

LADD A T KELLNER A and CORRELL J W Intravenous detergents in experimental atherosclerosis with special reference to the possible role of phospholipids *Federation Proc* Part I 8 360 1949

LEARY T Crystalline ester cholesterol and atherosclerosis *Arch Path* 47 1–78 1949

LOMBARD H L Personal communication

MORETON J R Physical state of lipids and foreign substances producing atherosclerosis *Science* 107 371–373 1948

MORRISON L M HALL L and CHANEY A L Cholesterol metabolism blood serum cholesterol and ester levels in 200 cases of acute coronary thrombosis *Am J M Sc* 216 32–38 1948

PONTICORVO L RITTENBERG D and BLOCH K The utilization of acetate for the synthesis of fatty acids cholesterol and protoporphyrin *J Biol Chem* 179 839–842 1949

RITTENBERG D and BLOCH K Utilization of acetic acid for synthesis of fatty acids *J Biol Chem* 160 417–424 1945

SCHOENHEIMER R and BREUSCH F Synthesis and destruction of cholesterol in the organism *J Biol Chem* 103 439–448 1933

SHEMIN D and RITTENBERG D On the utilization of glycine for uric acid synthesis in man *J Biol Chem* 167 875–876 1947

SNAPPER I Nutrition and nutritional diseases in the Orient *Advances Int Med* 2 577–605 1947

SPIES T D and BUTT H R in *Diseases of Metabolism* ed by G G Duncan 2nd Ed W B Saunders Philadelphia 1947

STEINER A Significance of cholesterol in coronary arteriosclerosis *New York State J Med* 48 1814–1818 1948

STEINER A and DOMANSKI B Dietary hypercholesterolemia *Am J M Sc* 201 820–824 1941

STEINER A and KENDALL F E Atherosclerosis and arteriosclerosis in dogs following ingestion of cholesterol and thiouracil *Arch Path* 42 433–444 1946

STEINER P E Necropsies on Okinawans anatomic and pathologic observations *Arch Path* 42 359–380 1946

WALKER W J Relationship of adiposity to serum cholesterol and lipoprotein levels and their modification by dietary means *Ann Int Med* 39 705–716 1953

WILENS S L The relationship of chronic alcoholism to atherosclerosis *J A M A* 135 1136–1139 1947

WILENS S L The bearing of the general nutritional state on atherosclerosis *Arch Int Med* 79 129–147 1947

ZIMMERMAN H M Personal communication

CHAPTER XI

The Oxidation Reduction Potentials of Saliva

It is known that a solution containing oxidizable or reducible substances shows a characteristic electrical potential In all solutions the electromotive force (EMF) is dependent upon the concentration of the solute the pH and the temperature But in body fluids oxidation reduction potentials (Ec*) are dependent not only on physical variables but also on the relations of enzymes coenzymes and substrates and their interaction with electrolytes (inorganic and/or organic salts) The potentiometer readings in millivolts of solutions of the latter type show a change with time which is referred to as drift in poise This is the result of the change in oxidation reduction potentials and may be altered easily by the addition of oxidants or reductants For further details concerning the mechanisms of enzymatic oxidations and reductions in cellular metabolism the reader may consult LuValle s and Goddard s excellent review paper (1948) and books by Michaelis (1925 1930) Hewitt (1936) and Lardy (1949)

Michaelis (1925) has reported on the initial oxidation reduction potential in whole blood Eisenbrandt (1943) studied the salivary potentials of five adults and found that the initial oxidation reduction values of his subjects did not vary significantly from each other in daily observations Eisenbrandt dealt primarily with the initial EMF values but did not emphasize them in relation to time

In a study to determine the degree of association between dental caries and the values of oxidation reduction potentials of fresh saliva (obtained without the use of physical or chemical stimulants) as a function of time it was found that among the children examined at Forsyth Dental Infirmary in Boston several dropped rapidly in their salivary potentials toward negative values These children appeared to fall into a distinct group and it was believed that further

Ec readings are the EMF readings taken directly from the Beckman potentiometer with the calomel platinum electrode combination, expressed in millivolts

investigation was merited Since the case histories were readily available, they were studied carefully It was found that among these children were some whose parents were particularly prone to degenerative cardiovascular disease This fact was made known to the members of the present project who then made further studies

Procedure

The studies dealt with 66 individuals who had had myocardial infarction and a group of 73 healthy working males roughly similar in age ethnic origin body build and mouth condition drawn from the matched control group Those taking the test had not eaten drunk, or smoked during the previous two hours Approximately 1 5 ml of saliva were collected from each person directly into a 5 ml beaker This freshly collected sample was placed immediately in a Beckman potentiometer (laboratory model G) with the standard Beckman calomel platinum electrodes inserted in position 1/16 inch apart in the saliva The door to the room was closed to ensure uniform atmosphere Readings were made directly from the designated scale on the instrument The salivary sample was kept inside the chamber with the electrodes fixed in the solution Readings were made first after 15 seconds and then at 1 minute intervals up to 5 minutes and following that at 5 minute intervals up to 30 minutes

In order to ensure experiments that would be reliable over a reasonable period of time and that could be duplicated repeated tests were performed on 6 'normal persons and on 3 patients who had had myocardial infarction

Duplicability of Patterns of Oxidation Reduction Potentials

Various patterns were found in the saliva The patterns differed in the numerical level of the oxidation reduction potentials and in the rate of change of the level with time Of the various possible combinations of starting potential and rate of change, the four in Figure 1 represent both the extreme and the modal patterns

The question arises immediately as to whether such differences as those shown in Figure 1 are stable Are the patterns characteristic of an individual can they be duplicated in that individual? In order to determine the reliability of the salivary oxidation reduction potential pattern several persons both normal and with coronary heart disease were tested over various periods of time

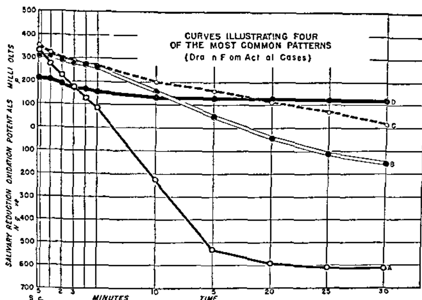


FIGURE XI–1 The four most common patterns of oxidation reduction potentials of saliva observed over a period of 30 minutes The majority of cases started at + 300 millivolts but the final readings on the Beckman potentiometer varied from + 100 millivolts to — 600 millivolts

A High positive at 15 seconds (> 300) to low negative at 30 minutes (— 600) rapid change

B High positive at 15 seconds (> 300) to moderate negative (— 150) at 30 minutes moderate change

C High positive at 15 seconds (> 300) to approximately 0 at 30 minutes slower change

D Moderate positive at 15 seconds (> 200) changing slowly but still positive after 30 minutes slow change

Coronary subject

A male married who had experienced a myocardial infarction at the age of 40 was examined on February 11 1949 and subsequently on May 24 1949 three weeks after an operation for a detached retina The test of the oxidation reduction potential of his saliva was repeated under oil on October 5 1949 This case illustrated the duplicability of results in the coronary population in that both the rate of change and the total drop were repeatable The individual minute readings matched less well Reliability and the possibility of duplication are necessary criteria for the application of the oxidation reduction potential testing procedure to saliva a medium that has been little surveyed by this technique The relia

TABLE XI–1 Potentiometer readings in millivolts of coronary subject (Year 1949)

Time	*2/11*	*5/24*	*10/5*
15 *sec*	+ 240	+ 245	—
1 min	+ 140	+ 222	—
2 min	+ 70	+ 192	+ 162
3 min	0	+ 172	+ 140
4 min	— 40	+ 156	+ 130
5 min	— 60	+ 138	+ 112
10 min	— 205	+ 20	— 100
15 min	— 570	— 114	— 315
20 min	— 576	— 261	— 438
25 min	— 576	— 377	— 451
30 min	— 578	— 451	— 471

bility of the technique under conditions similar to those outlined in this report is as good as may be expected in biological work. This degree of reliability is well illustrated in Table 1.

Control subject

A healthy male, aged 24, was tested twice on 2 successive days, given a respite for 5 days and then retested three times on 3 successive days. Following these five repeated tests, the subject was further tested at weekly intervals for 3 weeks, and finally after a month's freedom from testing was retested. All tests were administered at 10:00 A.M. In Table 2 the mean value and the actual values for each test time are listed. Note that the potentiometer values are relatively constant during this period of 58 days (March 15 to May 12).

TABLE XI–2 Potentiometer readings in millivolts of control subject (Year 1949)

Time	*3/15*	*3/16*	*3/21*	*3/22*	*3/23*	*3/31*	*4/6*	*4/13*	*5/12*	*Mean*
15 sec	+ 280	+ 282	+ 294	+ 300	+ 298	+ 296	+ 286	+ 290	+ 290	+ 290
1 min.	+ 272	+ 274	+ 278	+ 290	+ 286	+ 274	+ 278	+ 282	+ 284	+ 279
2 min	+ 262	+ 262	+ 274	+ 280	+ 281	+ 256	+ 266	+ 277	+ 276	+ 270
3 min	+ 254	+ 256	+ 272	+ 271	+ 273	+ 246	+ 249	+ 272	+ 269	+ 262
4 min	+ 250	+ 249	+ 264	+ 261	+ 266	+ 239	+ 251	+ 262	+ 261	+ 255
5 min	+ 244	+ 242	+ 261	+ 252	+ 266	+ 231	+ 248	+ 254	+ 254	+ 250
10 min	+ 228	+ 228	+ 242	+ 238	+ 231	+ 212	+ 222	+ 232	+ 230	+ 229
15 min	+ 212	+ 212	+ 232	+ 224	+ 227	+ 200	+ 208	+ 210	+ 194	+ 213
20 min	+ 201	+ 206	+ 225	+ 211	+ 218	+ 192	+ 198	+ 189	+ 180	+ 202
25 min	+ 192	+ 152	+ 221	+ 197	+ 211	—	+ 190	—	+ 172	+ 190
30 min	+ 178	+ 148	+ 212	+ 182	+ 203	+ 169	+ 182	+ 136	+ 164	+ 174

TABLE XI-3 Potentiometer readings in millivolts of coronary heart disease group of 66 males*

Time	*No in group*	*Range*	*Mean ± S E*
15 sec	66	+ 340 to + 100	+ 270 5 ± 5 93
1 min	59†	+ 330 to — 80	+ 239 0 ± 8 18
2 min	60	+ 292 to — 138	+ 213 0 ± 9 67
3 min	57	+ 284 to — 170	+ 179 5 ± 12 40
4 min	61	+ 278 to — 204	+ 157 0 ± 13 90
5 min	63	+ 272 to — 233	+ 133 5 ± 16 7[illegible]
10 min	60	+ 250 to — 550	+ 0 5 ± 28 77
15 min.	62	+ 232 to — 632	— 98 5 ± 33 76
20 min	61	+ 225 to — 642	— 156 5 ± 36 80
25 min	61	+ 220 to — 642	— 180 5 ± 35 89
30 min	62	+ 210 to — 648	— 246 5 ± 36 70

*Tests were not attempted on 31 males
†Occasionally readings were not obtained.

Oxidation Reduction Potentials in the Coronary and Control Groups

Oxidation reduction potentials were determined at intervals of from 15 seconds to 30 minutes in saliva from 66 males who had had myocardial infarction before the age of 40 and whose ages ranged from 25 to 52 at the time of examination and a control group of 73 healthy working males (mean age in both groups is 39) The mean results for each time interval are given for both groups in Tables 3 and 4

A statistical analysis of the data revealed a significant difference starting with the 2 minute value and extending through the 30 minute value

TABLE XI-4 Potentiometer readings in millivolts of control group of 73 healthy males

Time	*No in g oup*	*Range*	*Mean ± S.E*
15 sec	73	+ 352 to + 200	+ 280 0 ± 5 14
1 min	70*	+ 332 to + 150	+ 253 0 ± 5 41
2 min	69	+ 312 to + 100	+ 243 0 ± 6 19
3 min	67	+ 300 to 0	+ 20[illegible] 0 ± 6 76
4 min	63	+ 289 to — 50	+ 195 0 ± 8 11
5 min	73	+ 28[illegible] to — 100	+ 171.5 ± 9.23
10 min	73	+ 262 to — 358	+ 93.5 ± 16 49
15 min.	71	+ 252 to — 46[illegible]	+ 23 5 ± 2[illegible] 71
20 min	71	+ 246 to — 516	— 35.5 ± [illegible]8 09
25 min	69	+ 240 to — 530	— 85.5 ± [illegible]9 39
30 min	70	+ 240 to — 554	— 13[illegible]5 ± 30 23

O cas onally readings were not obtained.

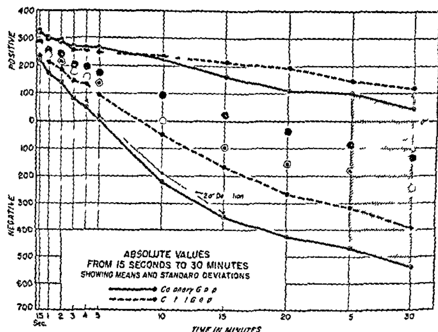


FIGURE XI–2 Oxidation reduction potentials of saliva in coronary heart disease group of 66 males and control group of 73 males The ordinate represents millivolts the abscissa, time in minutes The black dots and the circled dots represent the means at the various time intervals for the control group and the coronary group respectively

The data for both series have been put into graph form in Figure 2 Included are the mean values for each group at various time intervals and the ± 1 standard deviation limits for both groups Approximately 68 26 per cent of either group is included between these two limits

From the data plotted in Figure 2 several characteristics are at once apparent The general trend over a period of time for both groups was downward from a mean starting oxidation reduction potential of approximately + 280 millivolts to potentials of — 152 and — 246 millivolts respectively at 30 minutes The coronary heart disease group was distinguished by being below the control group at all intervals, hence the difference was systematic Furthermore the absolute difference between the two groups tended to be larger with elapsed time

In spite of the significant differences in the means there was a

broad overlap of the two groups as is evident from inspection of the ranges of values in Tables 3 and 4 The smallest overlap existed in time periods of from 4 to 15 minutes inclusive In fact during this interval the control mean minus two standard deviations was lower than the coronary mean minus one standard deviation with the result that only 2 27 per cent of the controls but 16 per cent of the coronary heart disease group fell below this point

The continual drift to negative values was common to both groups (Figure 2) Since the two groups started at approximately the same level and since the coronary heart disease group was much lower than the control group at 30 minutes it follows that the over all rate of change was greater in the coronary heart disease group

The total change during the 4 to 15 minute time interval was computed for each individual and the frequency distribution of this value was drawn for the coronary heart disease group and the con trol group Both distributions were markedly asymmetrical but the healthy control group was concentrated at smaller total changes (50 to 100 millivolts) whereas the coronary heart disease group showed no marked concentrations and in general showed greater changes

Interpretation of findings

How can the gross differences between the reducing intensities of the two groups as evidenced by the mean values of the oxidation reduction potentials be explained? The over all rate of change in activity was faster in the coronary heart disease group Such changes may be the result of absolute differences in concentration of various inorganic ions and/or combination of enzymes or coenzymes to gether with accelerators or inhibitors that may be present in the saliva

Van Potter (1949) has listed the following eight variables re sponsible for the in vitro control of enzyme activity temperature pH substrate concentration co factor concentration product con centration inhibitor concentration oxidation reduction potential and ionic strength Certain of these variables may be excluded from our consideration The temperature in these experiments remained at 22 ± 1 5 degrees centigrade thus the possible differences due to temperature are negligible The range of pH values of various

salivas tested was between 6 3 and 7 8 and while this may make some difference in the individual instance it was thought unlikely, because of the excellent buffering capacity of saliva that changes in pH produced the observed changes for the duration of these procedures

It has been shown that the coronary heart disease group differed from the control group in physique and in several biochemical properties When the physique and other factors were controlled through the use of the matched pair technique, the biochemical differences still existed The present chapter confirms the observations made in the previous studies that showed a basic biochemical difference between the two groups and is perhaps, more definitive in that the approach may involve basic enzyme systems

Using as the statistical lower limit of normality the conventional two standard deviations below the mean of the control group it was found that 16 per cent of the coronary heart disease group and only 2 27 per cent of the control group fell below this level in the 4 to 15 minute time interval Accordingly it was felt that apparently normal individuals whose salivary oxidation reduction potentials at 4 5 10, and 15 minutes fall below + 48 5 + 0 5 — 222 5 and — 360 5 millivolts respectively may show other characteristics of the coronary heart disease group and merit further study

Since the magnitude of the differences shown to exist in the salivary oxidation reduction patterns are of the same order as some of the other biological attributes of coronary heart disease this phenomenon may perhaps be considered to be as meaningful as the other biological attributes in distinguishing the person with coronary heart disease More concentrated study is indicated in order to isolate the differences in specific enzyme systems or inorganic ions of both groups of individuals

It should be emphasized that the reproducible phenomenon of oxidation reduction potentials of saliva cannot be explained satisfactorily with the evidence at hand No attempt is made here to explain it in terms of specific oxidation reduction systems or other phenomena which are known to affect these potentials However that there is a difference in these potentials of saliva between the coronary heart disease group and a healthy control group is apparent from the changes that occur in the potentiometer readings of saliva under the conditions described herein

REFERENCES

EISENBRANDT L L Initial oxidation reduction potentials of saliva *J Dent Research* 22 4 293–299 1943

HEWITT L F *Oxidation Reduction Potentials in Bacteriology and Biochemistry* 4th Ed London County Council 1936 P 101

LUVALLE J E and GODDARD D R The mechanism of enzymatic oxidations and reductions *Quart Rev Biol* 23 3 197–228 1948

MICHAELIS L *Oxidation Reduction Potentials* J B Lippincott Philadelphia and London 1930

MICHAELIS L *Practical Physical and Colloid Chemistry* W Heffer & Sons Ltd Cambridge 1925

Respiratory Enzymes ed by H A Lardy Rev Ed Burgess Publishing Co Minneapolis 1949

RODKEY F L and BALL E G Oxidation reduction potentials of the cytochrome c system *J Biol Chem* 182 17–28 1950

TURNER N C GERTLER M M and GARN S M Personal observations

VAN POTTER R The control of metabolism in *Respiratory Enzymes* ed by H A Lardy Rev Ed Burgess Publishing Co Minneapolis 1949 Pp 264–272

CHAPTER XII

Summary and Conclusions

THIS monograph presents the findings of a three year research program on coronary heart disease in young adults conducted at the Massachusetts General Hospital in the search for significant etiological clues The study represents the combined efforts of many individuals on diverse aspects of this disease entity In addition to 100 coronary heart disease patients under the age of 40 who had experienced myocardial infarction (at least six months prior to admission for the minimal 24 hour study), there were 146 unmatched controls A group of matched controls for the 97 male patients was also made up consisting of 74 men from the unmatched control group and 23 additional men

Clinical Appraisal

It is noteworthy that the clinical findings were not impressive Several items do however merit attention Only 5 patients (5 per cent) had arcus senilis this incidence is much lower than that reported by certain other investigators (Boas 1949), but it is in keeping with other observations of our own (Gertler and Garn 1950) Cardiac arrhythmias consisting of premature contractions only were observed in but 1 instance Paradoxical pulsations or diminished apical pulsations were observed in only 10 cases a much lower incidence than that reported elsewhere (Dack et al, 1940 Garland and Thomas 1948) Another interesting clinical impression was that as a group the patients appeared about 10 years older than their chronological age

Although the coronary patients consumed some forms of alcohol and used tobacco in statistically larger amounts than the control group the findings do not warrant any conclusions as to a causal relation between the use of alcohol or tobacco and coronary heart disease

Family Incidence

Heredity

The study of hereditary factors in coronary heart disease has disclosed several interesting facts The strong influence of heredity on coronary heart disease cannot be denied but the mode of gene transference or inheritance and the degree of penetrance have not been clarified by this study

The study of parental mortality revealed that at the time of the last interview 61 per cent of the parents of the unmatched con trol group were alive in contrast to 47 per cent of the parents of the coronary heart disease group Fifty eight per cent of the mothers and 35 per cent of the fathers of the coronary heart disease group were alive as compared with 73 per cent of the mothers and 48 per cent of the fathers of the control group Age difference in the parents was shown not to be the cause of this differential mortality

It is noteworthy that proportionately more parents of the coro nary heart disease group than of the control group died of cardio vascular disorders 51 3 per cent of the deceased mothers and 64 4 per cent of the deceased fathers of the coronary heart disease group as against only 35 9 per cent of the deceased mothers and 46 2 per cent of the deceased fathers of the control group

There were more deaths due to coronary heart disease in the families of the coronary heart disease group than in those of the control group Thus 9 8 per cent 37 1 per cent and 8 6 per cent of the mothers fathers and siblings respectively of the coronary heart disease patients died from coronary heart disease in contrast to 7 7 per cent 18 5 per cent and 1 0 per cent respectively of the mothers fathers and siblings of the control group

Race

Ethnic origin as an original factor in coronary heart disease was also considered in this study There were 27 patients of Jewish origin (26 men and 1 woman) 15 were strictly old Americans" 19 were various British Isles mixtures 12 were pure Irish 6 were pure English and 2 were Negroes The predominance of Jews in this series is in keeping with the observations of other investi gators the reason for it however is not clear It is known that Jews are particularly prone to diseases involving abnormal lipid metabo lism such as Tay Sach s disease Gaucher s disease and Niemann

Pick s disease This high incidence may in part be due to the high degree of endogamy in Jews Whether these observations may be extended to coronary heart disease cannot be answered by this research

Physique and Morphological Characteristics

The coronary heart disease group differed in certain special morphological characteristics from the control group These by and large with the exception of genital size (which is larger in the coronary heart disease group) may be attributed to the presence of mesomorphy (texture and a lower waist hip index) and a paucity of ectomorphy (less thigh interspace less knee interspace and more hip roundness)

There were significant differences between the coronary heart disease group and the control group in certain anthropometric measurements Generally the coronary heart disease group showed a decrease in vertical measurements an increase in horizontal measurements and an increase in depth measurements as contrasted with the control group The differing measurements may be summarized as follows (*a*) vertical—stature span total face length, hand length and chest length (*b*) horizontal—hand breadth and nose breadth (*c*) depth—upper chest depth and total chest depth One should be cautioned however not to define a 'typical coronary heart disease patient from anthropometric measurements alone

The somatotype findings in this study are illuminating and add greatly to our understanding of those further phenotypic expressions which are assessable only by biochemical analysis Hence the somatotype is invaluable if employed as a frame of reference to relate and correlate the biochemical findings (see below Biochemical Findings) The concept of such biochemical characteristics as a chemotype is another step in the definition of the normal physique its implications in disease have been discussed (Gertler, 1950) The coronary heart disease patients as a group were 44 per cent dominant mesomorphs and 6 per cent dominant ectomorphs as compared with the controls who were 22 per cent dominant mesomorphs and 18 per cent dominant ectomorphs It is noteworthy that the coronary mesomorphs were mainly *endomorphic* mesomorphs while the few coronary ectomorphs were *mesomorphic* ectomorphs

The finding that the young coronary heart disease patient is

usually an endomorphic mesomorph permits certain corollary observations and conclusions since the endomorphic mesomorph behaves differently physiologically and psychologically from other mesomorphs and other somatotypes (Sheldon 1940) Mesomorphs generally appear prematurely aged owing in part to their coarse heavy wrinkling Thus the clinical observation that the young coronary heart disease patients appear one decade older may be due in part to the normal older appearance of mesomorphy This tenet is reinforced by the observation that mesomorphs reach puberty 1 to 1 1/2 years earlier than individuals with other somatotypes Accordingly it is reasonable to suggest that mesomorphs at all ages are physically 10 per cent older than their chronological age (assuming that puberty occurs at 12 to 14 years)

According to published data there are a selected group of temperament traits and occupations which are associated with coronary heart disease The coronary patient is described as being a hard driving goal directed individual whose monodirective personality suggests refuge in work (Dunbar 1943) Some investigators have intimated that there is an excess of executive managerial and planning personnel in the young coronary heart disease group (Boas 1949) while still others have suggested a causal relation between occupation and coronary heart disease (Master et al 1939) Several questions may be raised on the merits of such a rigid classification and categorization Most reports on coronary heart disease come from urban centers where doctors are more accessible for any acute illness Accordingly, the medical records are apt to be influenced because (*a*) better records of patients are available to organized study groups and (*b*) few farmers or rural employed individuals are likely to be available to the urban physician and hence their medical records are rarely available for an organized study group and are likely to be excluded from any statistical analysis of coronary heart disease

If one employs the psychological and occupational correlates of mesomorphy adopted by Sheldon (1940) Hooton (1945) Seltzer (1945) Morris (1948) Fiske (1944) and Garn and Gertler (1950) one is impressed by the fact that many of the aforementioned descriptions of the young patient with coronary heart disease could easily fit the mesomorph The mesomorph enjoys participation in dangerous and strenuous undertakings he loves

speed he is hard driving and goal directed All these characteristics may account for the non conventional behavior pattern in the formative years of the coronary heart disease patients The mesomorph has a deep desire to be important in this world and to wield power over other beings and environment Such a trait may assume many garments of ambition such as those of executives managers army officers and the like Finally the striking preponderance in athletic ability is not surprising in the coronary heart disease group for there can be little athletic prowess in an individual who is not well endowed with the mesomorphic component

Athletic Activity and Occupations

The investigation of the relation of athletics and occupations to coronary heart disease yielded interesting information The coronary group scored higher in their athletic ratings than did comparable controls This fact might well be attributed to mesomorphy for it has been established that athletic prowess requires at least a rating of 5 in mesomorphy (highest rating possible is 7) It cannot be stated therefore that athletic participation is causally related to coronary heart disease for the presence of excess mesomorphy is merely the common denominator to the two characteristics namely athletics and coronary heart disease The study of occupations as related to the disease revealed a preponderance referred to above of individuals (42 per cent) in the managerial capacity Again it cannot be stated with certainty whether the risks mental strain and preoccupation of individuals in managerial positions are responsible for coronary heart disease or whether the ambitious driving nature which culminates in a managerial post is actually an additional causative factor

Masculinity

The question of masculinity in coronary heart disease has been considered at great length Several older observations have been confirmed several clinical impressions have been analyzed and quantified, others have been refuted and still others have been modified The ratio of 96 men to 4 women observed in a study of 100 cases of coronary heart disease under the age of 40 years by Glendy et al (1935) was essentially unchanged for in the present series of 100 cases there were 97 men and 3 women Thus the pre

dominant male element in this disease group under the age of 40 is the outstanding etiological clue The robust young male (White 1944) has been delineated as a male whose physical structure is that of an endomorphic mesomorph a heavily built bony mus cular and sturdy male A final appraisal of young males apparently most masculine will necessarily be postponed until further studies have been made Suffice it to say that these men were not psychologi cally the most masculine according to the Terman Miles test the coronary heart disease patients were less masculine in their final scores than the matched control group The coronary group actually achieved scores which were comparable to those of men ten years their senior and this according to Terman and Miles would indi cate a trend toward the typically feminine for as men become older their scores tend to assume the distribution usually ascribed to high feminine scores

At first it appears paradoxical that the coronary group as a whole appeared to be the most masculine according to physical attributes such as body build and secondary morphological char acteristics like hip roundness thigh interspace and hair distribu tion and yet did not appear to be highly masculine according to psychological appraisal It should be emphasized however that the physical and psychological aspects of masculinity are insignifi cantly related to each other As measured by the Terman Miles test psychological masculinity and femininity represent a composite of attitudes which stem from heredity social background and accul turation during life One must always keep in mind that the scores achieved by the coronary heart disease group could have been modified by (*a*) education and/or cultural level of the group and (*b*) the experience of being ill Accordingly the scores reported herein must be evaluated with some reservation at this juncture

It had been suggested from clinical observations that the young coronary heart disease patient is grayer balder and more hirsute in regions other than the scalp There proved to be no evidence however of increased graying in the coronary heart disease group frontal tonsorial and combined balding showed no significant dif ference from that in the control group There was no evidence furthermore of a significantly greater amount of body hair in the coronary heart disease group as compared with the control group The study did not concentrate on the relations of androgens to

hirsutism and no conclusions on this point may be drawn from the findings

The relation of urinary androgen excretion to masculinity has been studied by a number of investigators and has given rise to a great deal of speculation The evidence of lower sterone excretion in the 17 ketosteroid urinary studies cannot be interpreted as meaning 'less masculinity in the coronary heart disease group for (*a*) the lowered sterone excretion may be a result of the myocardial infarction, and (*b*) there is no definitive evidence that the urinary sterone excretion is associated or correlated with masculinity

Endocrine Findings

Endocrine studies were limited to a thyroid and a testicular adrenal survey based on 24 hour urinary sterone excretion The thyroid status was particularly studied in this young coronary heart disease group because of the possible influence of the thyroid on the course of coronary heart disease either through a causal relation with the abnormal blood lipids or through other unknown metabolic factors After studying thyroid influences with the aid of (*a*) basal metabolic rates (*b*) radioactive iodine uptake and (*c*) blood lipids it was concluded that there appeared to be a slight alteration in the thyroid activity from the euthyroid state in the direction of hypothyroidism Again it is not known whether this is a post hoc or a propter hoc phenomenon

The procedure of basing the testicular adrenal survey on the 24 hour urinary 17 ketosteroid (sterone) excretion is admittedly crude for it does not differentiate between secretions of the two glands but any alteration would be of interest as a point of reference There was however essentially no difference between the means of the daily urinary sterone excretion in the coronary heart disease group and in the control group Nevertheless certain findings are noteworthy There were *fewer* individuals in the coronary heart disease group whose daily urinary sterone value exceeded 14 mg while twice as many (17 per cent) of the coronary heart disease patients excreted less than 6 mg of sterone daily in their urine Furthermore the coronary heart disease patients who later died showed significantly lower daily urinary sterone excretions than either the rest of the coronary group or the unmatched control group

Biochemical Findings

The biochemical findings are to be evaluated in two ways first as etiological factors in coronary heart disease and second in relation to the somatotype findings

Cholesterol

The question of the causal relation between the level of total cholesterol in the serum and coronary heart disease was restudied and re evaluated The mean levels of serum total cholesterol in the coronary heart disease group the matched control group and the unmatched control group were 286 5 ± 6 6 241 9 ± 5 5 and 224 ± 3 5 mg per cent respectively While the mean values are significantly different the distribution curves are markedly continuous From this observation it is reasonable to infer that a threshold level of serum total cholesterol for coronary heart disease does not exist and that additional factors probably play a role

Lipid phosphorus and cholesterol/lipid phosphorus ratio

One of these additional factors appears to be the serum phospholipids The relation of the serum total cholesterol to the serum phospholipids seems to be an important factor in the etiology of coronary heart disease When the ratio of total cholesterol to lipid phosphorus was being studied it was found that in the coronary heart disease group the matched control group and the unmatched control group the mean values of the ratios were 22 4 ± 5 19 4 ± 3 and 18 7 ± 2 respectively In view of the increasing evidence that the colloidal stability of the cholesterol in the serum is dependent partially upon the ratio of total cholesterol to lipid phosphorus it was considered that this ratio had greater meaning in studying coronary heart disease than either of the components considered separately An additional confirmation of this hypothesis arose by deduction from the study of age changes and serum lipids It was revealed that both serum total cholesterol and serum phospholipids rise with age in both the coronary heart disease group and the control group However on analysis by the technique of partial correlations it was shown that when the influence of the phospholipids is removed in both groups the correlation between age and cholesterol disappears Moreover when the influence of cholesterol is removed the phospholipids continue to show a

correlation with age in the normal group but do not keep pace with age in the coronary heart disease group Thus a fundamental difference may exist in the two groups namely that in the coronary heart disease group cholesterol deposition in the intima may be enhanced by the lack of a colloidal stabilizer which may be due to a failure of the phospholipids to rise with age and hence to alter the total cholesterol/lipid phosphorus ratio

Uric acid

The question of the level of uric acid in the serum was considered It was found that the average value of serum uric acid in the coronary heart disease group was 5 13 ± 12 mg per cent in the matched controls 4 85 ± 07 mg per cent and in the unmatched controls 4 64 ± 06 mg per cent The differences between the averages of the coronary group and the two control groups were statistically significant It is of further interest that 22 per cent of the coronary heart disease group showed serum uric acid above 6 0 mg per cent while only 6 per cent of the unmatched control group showed serum uric acid above that level

Biochemical morphological relations

How do these chemical findings fit in with the concept of the morphological structure of coronary heart disease patients presented in this study? It will be recalled that the individual most likely to experience a myocardial infarction prior to the age of 40 is structurally an endomorphic mesomorph In relating variations in the levels of serum total cholesterol and serum uric acid to variations in physical structure several patterns were observed in the two groups

In the control group the highest absolute levels of cholesterol and uric acid were associated with the endomorphic physique and the lowest levels were associated with the ectomorphic physique The differences were statistically significant There was no significant difference between the endomorphic and mesomorphic physiques *in respect to these levels*

In the coronary heart disease group however two important changes were observed

1 The level of serum uric acid increased significantly over the control level in only one physique the endomorphic

2 On the other hand the level of serum total cholesterol in creased over the control level in each physique reaching its highest value in the coronary mesomorph in contrast to the lowest value in the control ectomorph

These two observations confirm and emphasize the original data on somatotypes The levels of serum total cholesterol and serum uric acid have their highest correlation with the mesomorphic and endomorphic dominances that are most typical of young adult coronary heart disease patients Accordingly it is reasonable to suggest that a metabolic relation is involved that is a tendency toward more frequent alteration in the metabolism of these two bio chemical factors in the mesomorphic and endomorphic physiques

Diet

The question whether dietary factors are causally related to coronary heart disease was investigated by studying the weekly ingestion of foods containing cholesterol and the relation of the ingested cholesterol to the cholesterol level in the serum of both the coronary heart disease and the control groups It was found that the patients with myocardial infarction had ingested on the average 3 3 ± 15 gm and the control group 3 9 ± 12 gm of cholesterol weekly It will be recalled that the average levels of serum total cholesterol for the coronary heart disease group and the control group were 286 mg per cent and 224 mg per cent respectively Thus the coronary heart disease group ingested less cholesterol than the control group but possessed more cholesterol in the serum It appears that the endogenous source of cholesterol plays a definite role in the etiology of coronary heart disease

Oxidation Reduction Potentials of Saliva

The study of saliva revealed several interesting phenomena The coronary heart disease group in contrast to the matched con trol group showed a faster rate of change per minute during the entire test procedure which lasted for 30 minutes but this was particularly noticed during the interval between the 4 minute testing and the 15 minute testing The average potentiometer readings of the coronary heart disease group at 4 minutes 5 minutes 10 minutes and 15 minutes were + 157 ± 13 9 + 133 5 ± 16 7 + 0 5 ± 28 8 and — 98 5 ± 33 8 millivolts respectively These

values are statistically lower than those observed in the control group which were $+195.0 \pm 8.1$, $+171.5 \pm 9.2$, $+93.5 \pm 16.5$, and $+23.5 \pm 22.7$ millivolts for the 4 minute 5 minute 10 minute, and 15 minute time intervals respectively

Conclusions

A great deal has been achieved with modern methods in the diagnosis of the acute or subacute phase of coronary heart disease which terminates in myocardial infarction However, the increasing death toll from coronary heart disease suggests that still another form of approach to the problem should be studied namely prevention It is obvious that before preventive measures are instituted recognition of the individual most prone to coronary heart disease will be necessary Efforts should be made to determine which individuals have the greatest tendencies to myocardial infarction How can we recognize these presumably abnormal people in the entire population?

The ability to prevent disease is generally proportional to the knowledge of the etiological factors and pathogenesis of a disease It is for these reasons that the problem of preselection of men prone to coronary heart disease from presumably normal males has been difficult in the past However in this study of persons who had experienced a myocardial infarction prior to the age of 40 certain leads were uncovered which may prove helpful in the recognition of those in whom myocardial infarction is most likely to occur

The suggested techniques are based upon evidence accumulated in this study which bears out the original thesis of the Coronary Research Project that coronary heart disease is caused not by one etiological agent but by many factors The multidisciplinary nature of the study has been most useful in that it has made it possible to select those characteristics which occur in the highest degree in coronary heart disease patients and to recognize them as potentially dangerous to any individual who possesses them (see Gertler et al 1951) By taking into consideration sex body build morphological characteristics heredity serum total cholesterol serum uric acid serum total cholesterol/serum lipid phosphorus ratio CUP index and salivary redox potential it should theoretically be possible to preselect coronary prone individuals from the population Since the

interrelations of many factors are involved in this method it probably has more merit than reliance on any single factor A long follow up study of the control groups should give us more evidence

It is hoped that as a result of the advances in preselection it may be possible in the near future to institute some form of preventive therapy to delay the episode of coronary attack At present there is to our knowledge no definite form of replacement or adjuvant therapy which has proved to be effective in this respect The difficulty stems partially from inadequate understanding of coronary heart disease and partially from lack of concerted effort in this aspect of preventive medicine We hope that clues to the solution of these two important problems will soon be found

REFERENCES

BOAS E P *Coronary Artery Disease* Year Book Publishers Chicago 1949

DACK S SUSSMAN M L and MASTER A M Roentgenkymogram in myocardial infarction clinical and electrocardiographic correlation *Am Heart J* 19 464–474 1940

DUNBAR H F *Psychosomatic Diagnosis* P B Hoeber Inc New York 1943

FISKE D W A study of relationships to somatotype *J Applied Psych* 28 504–519 1944

GARLAND L H and THOMAS S F Roentgen Diagnosis of myocardial infarction *J.A.M.A* 137 762–769 (June 26) 1948

GARN S M and GERTLER M M An association between type of work and physique in an industrial group *Am J Phys Anthropol* 8 387–398 1950

GARN S M and GERTLER M M Arcus senilis and serum cholesterol levels in the Aleut *New England J Med* 242 283–285 1950

GERTLER, M M The chemotype and the somatotype *Am J Phys Anthropol* 8 261–262 1950

GERTLER M M GARN S M and WHITE P D Young candidates for coronary heart disease *J.A.M.A* 147 621–625 1951

GLENDY R E LEVINE S A and WHITE P D Coronary disease in youth comparison of 100 patients under 40 with 300 persons past 80 *J.A.M.A* 109 1775–1781 1937

HOOTON E A Body build in relation to military function in a sample of the U.S Army (Report on contract W 44–109–QM–1078) Harvard University Press Cambridge Mass 1948

MALMROS H Arterioskleros och andra former av cholesteros *Nordisk Medicin* 42 1785–1791 1949

MASTER A M DACK, S and JAFFE H L. Precipitating factors in coronary artery occlusion further observations on mode of onset of a large series of cases with particular emphasis on the role of effort and excitement. *Indust Med* 8 327–331 1939

MORRIS C Individual differences and cultural patterns in *Personality in Nature Society and Culture* ed by C Kluckhohn and H A Murray Alfred A Knopf New York, 1948

SELTZER C C A relationship between Sheldonian somatotype and psychotype *J Personality* 16 431–436 1948

SHELDON W H STEVEN S S and TUCKER W B *The Varieties of Human Physique* Harper & Bros New York 1940

WHITE P D *Heart Disease* 3rd Ed Macmillan Co New York 1944

APPENDIX A

Terman Miles Masculinity Femininity Test

THE Terman Miles test was one of the tools used in the assessment of masculinity in this study The following excerpts are taken from the book *Sex and Personality* by Lewis M Terman and Catharine Cox Miles* to aid the reader in evaluating the test

Exercise 1 Quadruple choice Word Association

the subject s task in Exercise 1 is to underline that one of the four given associates following a stimulus word which seems to go best with the latter Each form of the M F test contains 60 stimulus words making 120 in all

In this and all the other exercises with the exception of Exercise 3 the present study of sex temperaments is based upon the weighted scores of the individual items which are given in Appendix IV [of Terman and Miles book] The weighted scores were used rather than unit scores in order that magnitude as well as direction of the sex differences could be taken into account

The population groups used in the derivation of weights for Exercise 1 included roughly 125 pupils of each sex in grade seven 100 of each sex in the junior year of high school and 50 college students of each sex in all about 550 subjects These are the subjects who furnish the data for our sex comparisons on Exercise 1

For purposes of convenience and also because they appeared more promising of results the responses to Exercises 3 4 and 5 were examined before those to Exercises 1 and 2 When Exercise 1 was taken up a number of hypotheses had already been reached with regard to the nature of some of the more important psychological differences between the sexes These hypotheses based upon an

examination of the responses of male and female groups to Exer cises 3 to 5 were utilized as a basis for forecasting the sex preferences of associations in Exercise 1 It will be interesting to see how adequately the explanatory hypotheses empirically arrived at from the responses in certain exercises explain the sex differences in exercises of a very different type

Exercise 2 Ink blot Association

In each form of the M F test 18 ink blots or drawings are pre sented and the subject is asked to underline one of the four words following each (the word that tells what the drawing makes you think of most)

The populations used in the analysis of responses to Exercise 2 were the same as for Exercise 1 We have tabulated the responses of the subjects in two ways one the less illuminative taking the associations absolutely the other by considering the more sharply contrasted associations in relation to one another and to the stimulus object The first tabulation which is self explanatory serves the former purpose

Exercise 3 Information Test

Each form of this exercise consists of 70 sentences (i e 140 in all) to be completed by underlining that word out of four supplied that gives the correct information required It is a quadruple choice information completion exercise success in which calls primarily for knowledge of fact and would seem therefore to depend upon the experience and interests of the subject Responses were analyzed for the same populations as in the case of the two previous exercises

We shall briefly summarize the results of our scrutiny before considering the detail

Within the range of the 140 items set and the subjects who responded to them a comparison of the sex preference scores indi cates that

1 Females show more knowledge
   (a) About domestic occupations
   (b) About matters of personal or household decoration adornment and etiquette
   (c) About literature (fiction) music (or rather musical technique) and conventional taste in colors

(d) Where the topic is one that appeals to one s active sympathy or feelings of tenderness (including in particular the maternal emotions)

2 Males show more knowledge

(a) Of extradomestic facts and events political social economic and business

(b) Of physical and scientific facts

(c) Of exploit adventure invention whether in fact or fiction

(d) Where the topic is one that appeals to the pugnacious aggressive or vigorously active tendencies

Exercise 4 Emotional and Ethical Response

Exercise 4 falls into six sections of which four concern occasions of anger fear disgust and pity respectively the fifth considers occasions of moral reprobation and the last compares preferences for alternative situations or types of occupation The analysis of Exercise 4 was based upon data from the following populations 148 boys and 172 girls in the seventh grade 116 boys and 128 girls in the junior year of high school and 50 college students of each sex in all 664 subjects

Exercise 5 Interests Likes and Dislikes

Exercise 5 is divided into eight series of likes and dislikes in the first five of which the subject has to declare whether he likes dislikes or is indifferent to

A Vocational occupations

B People with certain characteristics

C and D Certain forms of pastime entertainment occupations or situations

E Certain books

The last three series ask him which items from a given program he would like dislike or neither like nor dislike

F To draw (if an artist)

G To report on (if a newspaper reporter)

H To do or visit (if on a period of travel)

If the information exercise is an indirect this one is a direct inquiry into individual interests and to that extent would appear to obtain its results less from the accidents of experience and more

from the emotional dispositions of the subject and so to reflect more directly his actual temperament and personal habits of mind By actual we do not necessarily mean innate for our likes and dislikes are also influenced by environment

Our discussion is based upon data from 158 subjects in the grade school 200 in high school 52 in college and 80 non academic adults 590 in all Each group has an equal number of males and females

Exercise 6 Personages and Opinions

This exercise has two sections one calling for expression of attitude toward selected historical personages the other for judg ment of truth or falsity of certain statements Responses to both sections were analyzed for the following subjects 121 boys and 122 girls in the seventh grade 102 boys and 118 girls in high school and 50 men and 50 women in Stanford University a total of 563

Exercise 7 Introvertive Response

The exercise contains 42 questions in each form with Yes or No answers on tastes habits emotional and imaginative tendencies facts of experience and a few other topics many of the answers demanding self scrutiny In general they are of the type commonly used in tests of introversion or neurotic tendency The subjects were the same as for Exercise 6 except that the number of high school girls was 102 instead of 118

We may arrive at an index of preference (for an affirmative answer) by adding the figures under Yes and No and attaching to the sum the sign under Yes since the weights for Yes and No responses are nearly always the same and never differ by more than 1 e g

Do people ever say you talk
too much? + 2 Yes — 1 No gives a P I + 3 (male)
"Are you happy most of the
time? — 3 Yes + 3 No gives a P I — 6 (female)

SUMMARY AND CONCLUSIONS OF TESTS

Before concluding this inquiry with a brief discussion of the outcome it is desirable even at the risk of seeming tiresomely

repetitive to recapitulate its main findings exercise by exercise for their strength rests upon cumulative evidence rather than upon any single decisive experiment Taken serially they run as follows

Exercise 1 Word Association

1 If we take the associated words absolutely females pick more often than males upon terms for domestic things or things suggestive of kindly or sympathetic activities and much more often upon terms for articles or qualities of adornment and for colors males more often upon scientific and business terms and particularly upon terms suggestive of excitement and adventure and upon words for foods and each sex prefers names of persons of its own sex

2 If we take the items which show the most sex-contrasted responses divergences follow the same lines and also indicate a male preference for words signifying machinery common tools and outdoor pursuits

Exercise 2 Ink blot Association

3 Response words most obviously associated with machinery or science and with outdoor activities and adventure are picked upon more often by males more of those connected with domestic occupations and with aesthetic experience or personal adornment by females

4 When we consider the items which show the most sex contrasted responses the term which the stimulus figure evokes is in almost every case one connected with a common occupation distinctive of the responding sex

Exercise 3 Information

5 Females are more correctly informed about domestic occu pations domestic and individual embellishment etiquette fictional literature certain points of musical technique color shades and differences and on topics that appeal to active sympathy and maternal interest Males are more correctly informed about political business economic scientific and physical facts about exploits adventures and inventions and on topics that evoke aggressive and active bodily propensities

6 This divergence between the sexes is most marked in knowl

edge of facts or events that interest aggressive or adventurous dispositions on the one hand and maternally tender or sympathetic dispositions on the other

Exercise 4 Emotional and Ethical Response

7 Females express the most distinctive degree of anger on occasions of very unsympathetic or cruel treatment of human beings where help or sympathy is meet

8 Females tend to show a more distinctive degree of anger over school offenses and social vexations than over business and extra domestic troubles

9 The sexes diverge more in the fear than in the anger responses

10 Within the set of fear inspiring objects and situations presented the more fearsome the object the greater the female distinctive fear

11 Females express more disgust than males in general but particularly at disgusting male practices (repugnant habits of dress and person) at coarse language and at sexual immorality

12 Females express in general more pity than males but most for the weak helpless and visibly distressed especially where the object is a human being or a creature attractive in appearance and for cases of female more than of male distress

13 Females are in general more condemnatory than males but more noticeably in petty offenses and in offenses more common in males In negligible offenses on the one hand and very serious offenses on the other the sex distinction is inconsiderable

14 The severity of male censure increases more than that of female censure with increased gravity of the offense

15 Of the alternative occupations and objects presented for choice in the last section of the exercise males distinctively prefer the out of door and adventurous and the useful rather than the decorative females prefer indoor and urban conditions of living and things attractive in appearance rather than the useful

16 Females express more liking for working with men than men for working with women

17 Females tend to express a higher degree of the four emotions (particularly of disgust) and of moral censure than males

express but proportionately less in moral censure and anger than in pity fear and disgust

18 In general males record more defect of emotion and of moral censure than females particularly of disgust and fear with pity moral censure and anger following in that order

19 The interval between female excess and male defect averages greatest with disgust least with anger and moral censure

Exercise 5 Interests

20 The occupations for which females express a distinctive preference are the indoor artistic and decorative and the directly ministrative distinctively preferred by males are those entailing adventure bodily risk and muscular strength or prolonged exertion

21 Males distinctively prefer occupations undertaken predominantly by males females like male as well as female occupations

22 Females record a higher distinctive preference for predominantly female occupations than males for predominantly male occupations but also on the whole as high a preference for mixed occupations as males for male occupations

23 Throughout Sections *B* to *H* of this exercise a sex tends to prefer objects or topics which more particularly engage or concern members of that sex

24 Among the various types of material presented for response in Sections *B* to *H* males are found to express distinctive preference for experience implying adventure aggressiveness or interest in mechanical contrivances for out of door and physically strenuous occupations and for business commercial and political interests Females express preference for experiences evoking maternal tenderness or active sympathy and for aesthetic and domestically social experiences

25 In the aggregate female likes considerably exceed male likes and male dislikes exceed female dislikes but this holds of some sections more than of others In three sections of one form male exceed female preferences

26 In the aggregate male neutral scores (neither like nor dislike) exceed female considerably but (with one exception) this excess is confined to those sections in which female likes are most distinctive

Exercise 6 Personalities and Opinions

27 Females show a distinctive preference for women unfortunate people and philanthropists males for successful generals sports heroes and defiers of convention

28 Females distinctively believe statements favorable and disbelieve statements unfavorable to the female sex they subscribe to kindly males to rougher sentiments

Exercise 7 Introvertive Response

29 Males affirm distinctively tastes and habits that involve adventure or courage females habits or experiences that imply timidity active sympathy and care for personal appearance and with one or two exceptions they more readily confess weaknesses in emotional control and (less noticeably) of physique Females also admit more psychic abnormalities

30 Females more often than males give the introvertive type of response

We may now consider two questions to which the present findings give rise (1) Can we extract from them a single prime principle of sex difference at once not too vague to be ambiguous and not so particular as to be insignificant? (2) What so far as our evidence goes appears to be the relation of the differences we have enumerated to nature and nurture to endowment and environment? We shall take these questions in succession

1 *Is there one dominant principle?*

It is obvious that from whatever point we have started whether from the knowledge shown by the sexes or from their associations or their likes and dislikes for people vocations pastimes books or objects of travel or whether we have explored directly or deviously their emotions tastes opinions and inner experiences we have found ourselves arriving at much the same conclusions—all our ways have led to Rome But the final scene has two aspects—two sides of the same picture—one showing differences in the direction of interest the other differences in the direction of emotions and impulses

From whatever angle we have examined them the males included in the standardization groups evinced a distinctive interest in exploit and adventure in outdoor and physically strenuous

occupations in machinery and tools in science physical phe nomena and inventions and from rather occasional evidence in business and commerce On the other hand the females of our groups have evinced a distinctive interest in domestic affairs and in aesthetic objects and occupations they have distinctively pre ferred more sedentary and indoor occupations and occupations more directly ministrative particularly to the young the helpless the distressed Supporting and supplementing these are the more subjective differences—those in emotional disposition and direction The males directly or indirectly manifest the greater self assertion and aggressiveness they express more hardihood and fearlessness and more roughness of manners language and sentiments The females express themselves as more compassionate and sympathetic more timid more fastidious and aesthetically sensitive more emo tional in general (or at least more expressive of the four emotions considered) severer moralists yet admit in themselves more weak nesses in emotional control and (less noticeably) in physique

But we must define some of our terms more precisely for in stance aggressiveness and self assertion The evidence is for initiative enterprise vigorous activity outdoor adventure aggres siveness need not imply selfishness or tyranny or unfair attack The compassion and sympathy of the female again appears from the evidence personal rather than abstract less a principled humani tarianism than an active sympathy for palpable misfortune or distress In disgust in aesthetic judgment and in moral censure the evidence is rather for the influence of fashion and of feeling than of principle or reason Our evidence need not imply the possession of a truer taste or a more discerning conscience

But in asking how deep these sex distinctions go we reach our second question *What appears to be the relation of our main sex difference to nature and nurture to endowment and environment?*

The question is not let us remind ourselves whether this or that trait is innate or acquired for every human act or thought is both but whether the actual sex differences we are discovering are ascribable to biological (genetic) factors dividing the sexes or to sex differences in their training and environment So far as the evidence of our experiment goes we are not justified in ascribing the manifest differences to one alternative exclusively Certainly we do not have enough evidence to exclude the gross physiological

differences between the sexes from any part in determining the distinctive preference of the male for heavy muscular work and of the female for less active occupations or in determining her greater sympathy for the young and weak or her greater interest in home life with the relegation of outside interests to the male To actual or anticipated childbearing and motherhood—differences physiologically determined—we have found no reason to deny a part in determining differences in overt habits and emotional dispositions And in the present state of our ignorance it would be even more rash to deny the possible influence upon sex temperaments of the manifold differences between the sexes in their endocrine equipment and functioning

Whatever our view as to the innateness of the distinctive tendencies at least as to maternal tenderness in the one sex and comparative aggressiveness in the other our experimental evidence is inconclusive However when we examine the more direct manifestations of these and other contrasting tendencies in our exercises and consider how any particular manifestation comes about the power and reach of what we have named cultural sex bias its many plain and subtle effects on the upbringing and environment of the sexes within the groups we are considering keep coming to one s mind In so many ways too familiar to realize each sex gives and receives such different treatment as largely to explain the divergencies in expression or in fact revealed by the material we have studied Singularly powerful in shaping our development are other people s expectations of us past and present as shown by their practice and their precept Whether the boy is innately more aggressive and fearless more handy with the electric lighting than with the cooking stove more interested and informed about public affairs and about science more active and enterprising physically and whether the girl is by nature more sympathetic gentle timid fastidious more attracted to pots and pans than to rods and guns more punctilious in dress personal appearance manners and language at any rate society in the shape of parents teachers and one s own fellows of whichever sex expects these differences between the sexes and literature reflects them Irresistibly each sex plays the role assigned even in spite of its own protests The consequence is that throughout these several exercises however statistically consistent the distinctive sex responses may prove we cannot tell how

deep the difference lies—or how the deeper and shallower factors combine And here we must be content to leave the problem for it is clear that the deciding answer can be wrested not by a more meticulous struggle with this one set of exercises administered to groups comparatively homogeneous but from (1) parallel examinations of socially and racially different groups widely different in social tradition and circumstance, and (2) combined psychological and biological case studies of extreme deviants in sex temperaments within a given culture

APPENDIX B

Heredity Record

HEREDITY histories of both coronary patients and controls were recorded on the accompanying form, which may be used in con junction with a punch card system

MASSACHUSETTS GENERAL HOSPITAL

CORONARY PROJECT CARD 3

\# 1 2 3 SEX ______

NAME ______

AGE AT ONSET ____ 4( ) PRESENT AGE ____ 5( )

BROTHERS AND SISTERS ____ 6( ) BOYS ____ 7( )

GIRLS ____ 8( ) NO OF SIBS ____ 9( ) BOYS ____ 10( )

GIRLS ____ 11( ) AGE OF PARENTS

MOTHER (li g) ____ 12( ) FATHER (li g) ____ 13( )

MOTHER (d ad) ____ 14( ) FATHER (d ad) ____ 15( )

CAUSE OF DEATH OF MOTHER ____ 16( )

FATHER ____ 17( )

DECEASED BROTHERS OR SISTERS BROTHERS ____ 18( ) SISTERS ____ 19( )

CAUSE OF DEATH ______ 20

______ 21

HAVE ANY OTHER RELATIVES HAD HEART DISEASE ____ 23( )

CORONARY HEART DISEASE ____ 24( )

LIST ABOVE ([illegible]) ______

______ 25( )

NUMBER OF FATHER'S BROTHERS AND SISTERS ♀ ____ 26( ) ♂ ____ 27( )

MOTHER'S BROTHERS AND SISTERS ♀ ____ 28( ) ♂ ____ 29( )

DIRECTIONS: [illegible] only

CORONARY HEREDITY CHART

♂ ♀

GRANDPARENTS

PARENTS

EGO

SIBS

CONCLUSIONS ______ 30 ( )

APPENDIX C

Summary of Heredity Data

KEY

○ FEMALE

□ MALE
□ or ○ - PROPOSITUS
□ LIVING AT 32
□ Arth. = LIVING AT 32 ARTHRITIS
L 32 LIVING AT 32 (in parents and grandparents columns)
L 32 Arth LIVING AT 32, ARTHRITIS (in parents and grandparents columns)
D 32 DIED AT 32
□ D 32 DIED AT 32 CAUSE UNKNOWN
⊟ D 32 DIED AT 32 PNEUMONIA
D 32 Pn DIED AT 32 PNEUMONIA (In parents' and grandparents columns)
N O = NO ORDER ORDER OF BIRTH UNKNOWN
■ CORONARY ARTERY DISEASE
□ HYPERTENSIVE CARDIOVASCULAR DISEASE
⊠ CEREBROVASCULAR ACCIDENT Cerebral hemorrhage
□ EMBOLISM (pulmonary)
□ HEART DISORDER OF UNCERTAIN NATURE RHD

Acc	ACCIDENTAL DEATH
Add.	ADDISONS DISEASE
Arth.	ARTHRITIS
Asth.	ASTHMA
Ca.	CANCER
Ch.B.	CHILDBIRTH
Db	DIABETES
Epil.	EPILEPSY
Fist	FISTULA
Gallb.	GALLBLADDER DISEASE
Hyc.	HYDROCEPHALY
D Inf	DIED IN INFANCY
Infect Sep	INFECTIONS Diphtheria Scarlet Fever Meningitis etc
Liver	LIVER DISEASES Other than Cancer
Lues	LUES SYPHILIS
Park	PARKINSONS DISEASE
PA	PERNICIOUS ANEMIA
Pn	PNEUMONIA
Ren	RENAL DISEASES (glomerulonephritis)
RHD	RHEUMATIC HEART DISEASE
TB	TUBERCULOSIS
Typhd	TYPHOID
Xanth	XANTHOMATOSIS

CORONARY HEART GROUP

NO	MOTHER	MOTHER S MOTHER	MOTHER S FATHER	FATHER	FATHER S MOTHER	FATHER S FATHER	PROPOSITUS & SIBLINGS	♂ ♀
001	L 68	D	D 70	D 64 [8]		D 50 ▨	[48] [40]↙ [39] (36)	3 1
002	D 40s (▨)			D 40's			[47]↙ [▨ ▨ [Db] (Db)] D 40's [ ] D 1	5 1
003	D 51 Ca	D	D	D 53 ▨	D 79	D 50 Acc.	▨ D 40 [47]↙ (46) (44) [43] (39)	3 3
004	D 65			D 77 ■	D 79		[3]↙	1 0
005	L 55	D 75 (CV)		D 55 ■	L 81	D 59 ■	[39] [3]↙ [33] [27]	4 0
006	D 65 Infect	D 30s Ch B		D 33 Acc			[48] (Sep) D 1 [Sep] D 1 f (43) [40]↙	3 2
007	L 73			D 72 Acc			[40]↙ 3 [?] 2 (?)	NQ 4 2
008	D 54 (CV)	D 60	D 90	L 62	L 80's	D 90	[37] [35]↙ (31)	2 1
009	L 69 ○	D 39 Acc	D 45 Acc.	D 68 ▨	D 81	D 45 [CV]	[48] (46) [CV] D 35 (44) [42] (40) (38) (37) [35]↙ [33] [ ] D Inf (30) [Acc] D 20 (25)	7 7
010	L 62 ○	D 70s	D 50s	L 65 ■	D 70s	D 70s Pn	[4]↙ [41] (39) (37) [38] (33)	3 3
011	L 61	D 58 Gallb	D 51 Pn.	D 51 Pn	D 65 Db	D 70's	(45) [43] [0]↙ (37) (35) (33) (30)~(30) [28] (2) [19]	4 7
012	D 58	D	D 42	D 55 ■	D 72	D 74	[Acc] D 39 [43] [42]↙ [36]	4 0
013	L 59	D 41 Ca	D 60s ▨	L 60	D 60s Ca	D 70s	[42]↙ (37)	1 1
014	L 70	D 20 Ch B	D 90s	D 67 ■	D 80	D 63 ■	(9) (8) [5]↙ [38]	2 2
015	D 64 (C)			L 83			[Sed] D 2 ○ [ ]↙ ○	2 2

016	D 86 Pn	D	D 80s	D 64				5 2
017	D 49	D 39	D 71 Ca	D 41	D 70	D 82 Acc	D 38	2:1
018	L 73	D	D 75	D 52	D	D 50	D 38	5 2
019	L 56 Gallb	D 33	D 65	D 60 Ren	D 70	D 75		2 0
020	L 62			L 65				3 4
021	D 72			D 54				2 0
022	L 72	D	D	D 58	D	D		4 0
023	L 65 Arth.	D 62 Typhd	D 40	L 65	D 70	D 55		2 1
024	D 59	D	D	D 55	D	D	G 118	4:4
025	D 49	D 68	D 68	L 63	D 72	D 76	D Inf	NO 3 3
026	D 36			L 58	D 90	D 85	RHO; D 29; D 1	2 2
027	L 68	D 68	D 38 TB	D 65	D 68	D 75		4 1
028	D 44	D 75	D 75	L 59	D 20s ChB	D 49 Acc	D 20	5 3
029	D 38 Pn	D 60s	D 89 Ren	D 64	D 50s	D 87 Ca	D 55; D Inf	NO. 3 1
030	D 38 Acc	D 82	D 87 Ren	D 30 Acc	D 50	D 70		2 0
031	L 66	D	D	D 64	D	D		4 3
032	L 55			D 47 Pn	D 80			3 0
033	L 69			D 54			D 1; D 11	6
								6
034	L 68 Ca	D 51 Asth	D 89 Pn	D 58	D 58	D 60	D 11	2 5

NO	MOTHER	MOTHER S MOTHER	MOTHER S FATHER	FATHER	FATHER MOTHER	HER'S FATHER	PROPOSITUS & SIBLINGS	♂ ♀
035	L86			D38			57 G llb, 55, 46 A th, 44	2 2
036	L65	D77 (CV)	D72 ▨	L67	D60s	D70s	○ D44, Hy D2, 39, 36	2 2
037	L63	D35 Ch B.	D70 Acc	L65	D85	D40	42, 41, 34, 31	4 0
038	D53 ●			D62 ■			■ D45, ?, ?, A c D?, ? N Od, ?	4 2
039	L63	D86	D70	L64	D92	D49	45, 4, 39, A D20, 34	4 1
040	D44 Ca			D48 ▨			36, ■ D?, □ D35, ?, ? N Od	3 2
041	D49 (CV)	D61 (CV)	D64 Ren	L69 □	D30s	D40s	4, 42, 40, 37, 29, 25	6 0
042	D62 ▨			D36 ▨			63, 61, S p D22, 48	2 2
043	D62 Ren			D53 Pn			56, 43, □ N Od	2:1
044	D52 Pn		D88	L72		D90	48, 6, 44, 11, 39	2 3
045	D67 (CV)	D70 Ca	D80 Infect	D67 ■		D60	55, □ D11, 50, 48, 43	4 1
046	L69	D76	D76 Ren	D76	D38 ▨	D40s Pn	36, 33	1:1
047	L54 ○			D62 ■			■ D36, Db D4, Db D12, ?, ? N Od	3 2
048	L71 Arth	D60 Ca	D □	D53 CV	D60 Ca	D74	43 X th, ● D40	0 2
049	L64 Psy			D64 Lues			■ D42, Db, ?, Psy, ?, ?, ?, ?	5
							?, Sep D5 N Od	5
050	L54 Gallb			L55			53, ?, ?, ?, ?, ? N Od	4 1
051	L62			L65	D82		39, 38, Sep D17, 34, 31	2 3
052	L75 Arth.	D81 Pn	D76	D71 ■ Db	D46 Pn	D72	44, 42, 8, □ S llbe N Od	3 1
053	L57 ○	D70 Gallb	D59	L66 Db	D	D52 ▨	32, 30, □	2 1

054	L 55	D 80s	D 50s	D 55	D 30s Acc	D		2 1
055	L 65	D 40 Typhd	D 42	L 72	D 72	D 74		1 1
056	D 80	D. Ch B	D 40 Ren	D 72	D 72	D 85	D 7 D 5 D 20 D 7 N Cv	7 0
057	D 36			D 70s Ca				2:0
058	L 75 Ren			D 59			N D #	3 0
059	L 69			D 59 Ca				1 3
060	L 58	D 70	D 62	D 62 Pn	D 70	D 70	Stillborn	2:1
061	L 74	D 60	D 70	D 80's Pn	D 70	D 80	D 25	2:2
062	L 59	D 88	D 62	L 57	D 35 Ch B	D 69		7
								7
063	L 75	D 70	D 80	D 67 Acc	D 80	D 80	Db CV D 36	4 1
064	D 38 Pn			D 58				3 2
065	D 53	D 64	D 73	D 56	L 83	D 60s		1:0
066	D 65 Ca			D 68			N Drd Acc D 7	3 5
067	L 66	D 30 Ren	D 60s	D 60	D 60s	D 83		1 0
068	L 68	D 65 Ren	D 68 Ren	D 84	D 87	D 70	D 3 D 11	4 0
069	L 57 Ren			L 67			N D #	1 2
070	L 75			L 77	D 83	D 84		3 1
071	D 52			L 86			D 34	5 3
072	L 63	D 20	D 70	D 68	D 30	D 30		1:0

(Coronary Group—continued)

NO	MOTHER	MOTHER'S MOTHER	MOTHER'S FATHER	FATHER	FATHER'S MOTHER	FATHER'S FATHER	PROPOSITUS & SIBLINGS	♂ ♀
073	D63 ○ A	D60 ○	D70	D50 ■	D 80	D50 ⧄	(45) Pn D I f [3]	2 1
074	D65 (CV)			D55 Pn			[4]↙ [?] [?] (?)	3 2
075	L 64	D 82 Ca	D 70s Acc	D 40 □	L 90's	D 60s	[43] [40]↙ [37] (29)	3 1
076	D72 (CV) Db			D 80 [CV]			[63] (60) [5] (3) [49] (47) (41) [39]↙	4 4
077	L.60	D 32 Ch B	D.71	L 64	D 80 ●	D 86	[C] D 40 [38]↙ [36] [34] [26] (23) (20)	5 2
078	L.73	D.73 ▨	D 60 Ren	D 57 Ca	D 60's	D 70	[43] [39]↙ [36]	3 0
079	D60 (CV) Arth.			D.76 ■			[49] [46]↙	2 0
080	L.59	D 70 ○	D 96	D 49 Ca	D 65	D 99	[41] R [39]↙ [37] (22)	3 1
081	L 68 Db	D 60 Pn	D 72 Ca	L 67	D 60 ▨	D 45 Pn	[TB] D 45 [45] (43) [40] [39] [35]↙ (TB) D 25 (TB) D 25	5 3
082	D72 (CV) Ath			D 65 ▨		D 80s	(32) (ChB) D 45 (Pn) D ? (P) D ? [37]↙	1 4
083	L 69			L 71			[47] [43] [41] [38]↙ [34] [Acc] D2 (26)	6 1
084	L 70 ○	D 40 Ca	D 78 Ca	D 54 ■	D 69	D 78 Pn	[43] [40]↙ (38) [36] [33] (26)	4 2
085	L 58 ○	D 83		L 65	D 42	D 62	[37]↙ [35] (32) [24] [22] [15]	5 1
086	D 50s			D 60s Pn			[C]↙ (25)	1 1
087	L 62	D 70s ▨	D 69	D 55 ■	D 70s Ca	D 50s	(39) [37]↙ [35] (33) (31) (28)	2:4
088	L 65 (CV)			D Pn			[39]↙ (3.) □ D I f N Ord	1 2
089	D 45 ○	D 58 Ca	D	L 65	D 43 Infect.	D Fist	○↙ [38] (35) R [28]	2 2
090	L.68 Db	D 82	D 39	L 73	D 75	D 75	(43) Db [38]↙ (Pn) D 35 (33) [29]	2 3
091	D 51 ○	D 60s ○	D 65 Pn	L 55	D 60	D 70	[30]↙ [28] (26) [2] [21] (17) [12] [10]	6 2
092	D 70 ○	D 70's	D 60s	D 84	D 40's	D 84	(5) [5] (2) (6) [6]↙ (1)	2:4

093	D 47 Db			D 66 ■			(53) c (51) [9]↙ [ ] Dif [39]↙	3 2
094	L 61	D 68 Pn	D 60s Infect	L 61	D 80s Ren	D 80's Pn	[35]↙ [28]	2 0
095	D 35 ⊘			L 70s [C] Db			(40) (35) (30) [25]↙	1 3
096	D 29 Pn	D 83	D 70 Acc	D 47 ⊡	D	D 65 Infect	(39) [37] ○ Dif [35]↙ ○ D Birth	2 3
097	L 51 Gallb		D 70	L 55		D 63	[33]↙ [29] [22]	3 0
098	L 55 ○	L 80	D 47	L 58		D 54 Ren	(33) [30]↙ (20)	1 2
099	L 69			L 70			[44] [42] [40] [39] [3]↙ [25] (21)	6 1
100	L 69 Arth			L 65			[41] [38] [36] [31]↙	4 0

(Coronary Group—concluded)

UNMATCHED CONTROL GROUP

NO	MOTHER	MOTHER S MOTHER	MOTHER S FATHER	FATHER	FATHER S MOTHER	FATHER S FATHER	PROPOSITUS & SIBLINGS	♂ ♀
001	L 58	D 60	D 55 □	L 63	D 78	D 93 □	□27↙ ○25 □23 □21	3 1
002	D 74 ○			D 72 Ca			□? ○? ○? ○? ○? ○? □Acc D 27 ○Sep D 18	3
							○Sep D 12 □37↙ N Od	7
003	L 75 Arth Db	D 70	D 80	D 30 ■	D 60	D 70	□48 □45↙ □43 [□ □ □] D 1 ? N Od ○ D 6	6 1
004	L 75 Arth	D 85	D 85	D 54 ■	D 80		○46 □44↙	1 1
005	L 62	D 50	D 55	D 60 □CV	D 80	D 45	□3 □30 □28↙ ○26 □24 □21 □18	6 1
006	D 70	D 90	D 40	D 72 Arth ▨	D 90	D 90	□C D 45 ○48 ○47 ○43 □42 ○41 ○40 □37↙	4
							□ D 1 ? ○34 ○28	7
007	L 48	L 70	D 60 □CV	L 51	D 60	D 60 Ca	□25 □22↙ ○ D 1 ?	2 1
008	L 59	D 63 Pn	D 67 □	L 63	L 81	D 83 □CV	□28↙ □22 ○Db D 1 ? Ne Ord	2 1
009	D 50 Ca	D 62 Ca	D 47 □CV	D 47 Ca	D32 Typhd	D 76 Ca	□38 □30↙ ◇ D.81 th	2 0
010	L 63	D 88	D 62 □	D 57 ■	D32 Ch B	D 50 ▨	○40 □37 □36↙	2 1
011	L 61	D 75	D 75	D 58 □	L 85 Db	L 88	□32 □31 □29 ○27 □24↙ □21 □ D 1 ? N Orde □ D 1 ?	7 1
012	L 62			D 56 Ca				3 0
013	L 57	D 30 TB	D 66 Ca	L 56	D 30 TB	L 94	□34 ○33 ○33 ○32 ○31 □29↙ ○21	2 5
014	L 65 Arth	D 80	D 80	L 76 ■	D 90	D 98	□29↙ ○ D 81 h	1 1
015	L 80	D 35 TB	D 82 □CV	L 88	D 45 Pn	D 60 ■	□↙ □? □TB □TB D 27 ○C D 47 ○? N Od ○? ○?	4 4

016	D 54 Ren			L.66			○ □ □ ○ □	3 2
017	L 62 (CV)	D 81	D 60 [E]	L 61 Arth	D 60 Acc	D 60	□ ○ ○	1 2
018	L 76			D 45 Acc			2 9 4 40 30 ○ □ □ □	6 3
019	D 67 ●	D 60	D 50	L 68	D 60	D 50	46 4 2 41 0 35 27	6 1
020	L 56	D 83		L 56			2	1 0
021	L 59	L 88	D 50	D 69 ▨	D 60 Arth.		29 27	1 1
022	L.74	D 87	D.86 Pn	L 76	D 89	D.85	44 40 39 56 □ □ □ 35	5 3
023	L.53	D 28	D 76 [CV]	L.57	D.72 Gallb.	D 75 Ca	38 56 33 31 26 □	4 2
024	L.69 Arth	D 69	D 71 Pn	D.74 □	D 60	D 70	(CV) D 34 42 40 37 30	3 2
025	D.45 Pn	D 80	D 60	L.72	D 60 Acc	D 81 Acc	37 34 31	2'1
026	L.51 Arth.	L 73	D 76 ▨	L 57 ■	D 50 (CV)	D 86 [CV]	31 29 27	3 0
027	L 61 Db	D 68 Db	L.86	L 62	D 75 (CV)	D 81	36 35 ○	2 1
028	L 56 Db		Db	L 59			36 35 33 31 Acc D.24 ▨ D.27 22	4 3
029	L.52			D 50 ■			◇31 ◇30 ◇29 28 ◇27	2 3
030	L.74	D 70 ⊘	D 40	L 74 [CV]	D 34 Ch B	D 50 Acc	(Acc) D.37 36 Acc D 33 3 32 A	3 3
031	L.59 Arth	D 68 Ca	D 72 ■	L 61 Ren	D 83 (CV)	D 53 ▨	1 32 26	1 2
032	L.65 Arth	D 63		L 65			39 37 35 29 □	2 3
033	D 81 Pn	D 60 s	D 60 s	D 65	D 60 s	D 60 s	Acc 66 6 63 ○ D 18 (CV) D 56 (Sep) D 28	5
							52 50 48 42	6
034	L.70	D 60	D 50	D 73 ■	D 50	D 69	46 42 39 ○	2 2

NO	MOTHER	MOTHER S MOTHER	MOTHER S FATHER	FATHER	FATHER S MOTHER	FATHER	PROPOSITUS & SIBLINGS	♂♀
035	L 75	D60 Pn	D93	L 80	D70	D 70	57 [ ] 55 [ ] (5 (8) ( ) D11 [46] (Acc) D? [42] [38]↙ (Sep) D 7 [33]	8 5
036	L 76	D88	D 70 ■	D79	D 75 (CV)	D 75	[42]↙	1 0
037	L 65	D 25	D 50	D 63 Db	D 80	D40	( ) D11 [37] (35) [31]↙ (30) (28)	2 4
038	L 56	D69 Ca	D 36 Typhd	L 58	D47 (CV)	D 75 Ren	[34]↙	1 0
039	D53	D 60	D 60	L55	L 78		[28]↙ (25) (23) [16] [( ) ( )] D11	2 4
040	D57 T.B.			D 55 TB			(39) [36] [31] (30)	2 2
041	D 73 ◍			D76 ▨			◍ D50 [49] [47] (44) [42] [40] [39]↙ N Order [[ ] [ ]] D11	7 2
042	D 64 Ca.	D78 Pn	D.37 Ren	L.69			[38] [35]↙	2 0
043	L 62 ○	D 36	D76	L 75 Db	D 70s	D 78	[ ] D11 [36] [35]↙ [33]	4 0
044	L.53	D82	D 89	L.64	D62	D 78	(34) [32]↙ (29) ( ) D11 N Od	1 3
045	L 64	D80	D 70	L 65 Db	D 70	D.60 s	(39) [38]↙ [31]	2 1
046	L.71	D 94	D 90	D 72			[41]↙ [43] (40) [38] (38) [35] (31)	4 3
047	L 55	D 28 Ch B	D 73	L 55 ⬚	D 75	D 75	(33) [30]↙ [27] ( ) D11 N Ord	2 2
048	D 75	D 36 Ch B	D 80s	D 69 ■	D 76	D 60s Pn	[4]↙	1 0
049	D 52 (CV)	D 75	D 80	D 52 Infect	D 60		[9] [44] (42) [40] (30) 6 [ ] a ( ) a ( ) a	9 4
050	L 76			L 80			(Sep) D18 (50) (48) [45] (41) (C) D39 [35] [33] [30]	4 5
051	L 68	D 48 Pn	D 54 TB	L 71	D 50	D 45 Acc	(Sep) D2 [42]↙ (40) [38] (36) [34] [26] ◍ D16	4 4
052	D 28 Infect			D 62			(5) [40]↙ [Sep] D? N Order	2 1
053	D 70 ●	D 87 ◍	D 65 Ca	L 74	D 70 Ca	D 78	[8] D 40 [ ]↙	2 0

054	L62	D91	D72	D36 Ca	D66	D73	□	1 0
055	L74	D30's	D92 Pn	D56 Acc	D30s	D82 □	□ □ □	3 0
056	L46	D. (CV)	L85	D47 ■		L78 ■	□ □ □	3 0
057	L71 Arth	D51		D41 Infect	D58 Ca	D67 Pn	(43) (0) [3] ◍ DIf	1 3
058	L64	D75	D65 [CV]	D37 Pn	D78	D84	[38]	1 0
059	D49 Pn			D50 Ca			[36] [?] (?) (?) □ DIf ○ DIf N Od	3 3
060	D54 (CV)	D50s	D60s	L67	D60s	D70s	[44] (41) [38] [36] (34) [32] (30) (24)	4 4
061	L53	D31	D69	L55	D50	D63	[30] (28) (23) [19] [12] ◍ D9	3 3
062	D46 Ren			L63	D60s	D80s	[28] [24] [22] (19) (16) (16) □ DIf N Ord ○ DInf	4 4
063	L60 Arth	D75 (CV)	D74 Ren	D55 TB	D56 Infect	D72 Acc	[38] (TB) D35 [33] [26] 2□ DIf N Od ○ Q Birth ○ Bl B by	5 3
064	L48	D64	D68	L64	D65	D72	[30] (29) [24]	2 1
065	L60	D80 (CV)	L86	L64	D86	D67 □	[34] (31)	1 1
066	L60 ○	D66 Pn.	D70 [C]	L66	D74 ◍	D71 Pn	[35] [3] (28)	1 2
067	L56	L81	D54 □	L59	L98	D82 ◍	[3] (30)	1 1
068	L75 Arth	D60's	D70s	D68 ■	D60's	D50s ■	[42] [40] [38] (36) [34] [32]	5 1
069	D50 ○			D50 Ca			[4] [41] (39) [37] [35] [C] D? (P) D?	7
							○ DIf 2□ D? N Od	3
070	L63 ○	D76 Gallb	D48 Acc	L71 Ren	D50s (CV)	D60s Acc	[39] [31] [S.D] DIf N Od	3 0
071	L87	D87	D40 Infect	D84	D38 Acc.	D67	(53) [50] [48] [44]	3 1
072	L69	D72	D83 Ca	D49 Acc	D65 (CV)	D71 Ren	(32) [31] (30) (30)	1 3

(Unmatched Control Group—continued)

NO	MOTHER	MOTHER S MOTHER	MOTHER S FATHER	FATHER	FATHER S MOTHER	THER HER	PROPOSITUS & SIBLINGS	♂ ♀
073	L 60 s	L 82	D 84	L 60 s	D 83	D 70 s	[illegible] [illegible] [35] [28]↙	2:2
074	L 59			L 69			[33]↙	1 0
075	L 52	D 69 Ca	D 86 ⬚	D 33 Acc	D 55 Ca	D 80	[33] [29] [27]↙ (26) (24) [Sep] D 6	4 2
076	L 63	D 60 s	D 50's	L 65	D 40 s	D 50 s	[42]↙	1 0
077	L 72	D 70 Pn	D 72	L 73	D 35	D 76 Pn	[39]↙ (37) (34) [32]	2 2
078	L 42	L 69	D 60 ■	L 52	L 89	D 83	[2]↙ (20) (19)	1 2
079	L 60 ○			D 35			(Acc) D 27 [38]↙ [36] (34) (32)	2 3
080	L 67	D 90	D 98	L 68 Db	D 79	D 68	[45]↙ (38)	1 1
081	L 55 ○	D 50	D 80	L 60	D 80	D 85	[35] [33] [32]↙ [30] (28) (26) [24] (22) [20]	6 3
082	L 54	D 82 Acc	D 86	L 59	D 70	D 84	(30) [28] (25) [22]↙ (18) (14) [10]	3 4
083	L 41	L 60 s	D 50 s ▨	L 52 ⬚	D 70 s Db	D 70 s Db	[26]↙ [21] [6]	3 0
084	L 74	D 70's	D 70's	D 72 ▨P	D 67 ◍	D 68 TB	(40) [37]↙	1 1
085	L 55	D 83	D 75	L 60	D 50 Acc	D 77 Pn	[32]↙ [30] [28] N Od [ ] D Birth [ ] D 1 r [22] (18)	6 1
086	L 77			D 77 Ca	D 83 ◍	D 81 ▨	[53] [50] (46) (44) (42) [35]↙	3 3
087	L 68 ○	D 87 ◍	D 87 ⬚	L 68	D 60 s	D 83 ▨	[36]↙	1 0
088	L 66	D 59	D 65	D 76 ■	D 80	D 69 CV	[35]↙	1 0
089	D 42 Infect			L 73			[Acc] D 35 (Sep) D 8 [30]↙ (28) N Od	2 2
090	L 51 Arth	D 44 ◍	D 63 C	L 56	D 82 Acc	D 72 Ca	[33]↙ [Acc] D 31 (TB) D 27	2 1
091	L 64	D 72		D 63 CV		D 70	(42) [41] [39]↙ (37)	2:2
092	L 72 Arth	D 70's	D 74	L 76 ▨	D 90's	D 40 s TB	[M] D 1 r (Pn) D 1 r [2] (40) [ ]↙ [36] (33)	4 3

093	L63	D60s	D50s	L65	D88	D85	(40)	1 1
094	D48 ○	D72		D56 Infect			○ □✓ ○ (34)	1 3
095	L62 ○ m		D84	L64		D30s	[36]✓ [34] [3] □ [30] [?] (?) (?)	6:2
096	D73 Infect			D50 [CV]			[4]✓ □	2 0
097	D42 Infect	D60s	D64	L65 [CV]	D64 ○	D44 Acc	[0] R 14 [33]✓	2:0
098	L67	D57 Infect	D84 Acc.	L76	D88 Ca	D74 Infect	(45) [44]✓	1:1
099	L77 Arth	D88	D89	D81 PA	D68	D84	[44]✓	1 0
100	L68 ○ Arth	D84	D50s Asth.	D51 Arth	D60s	D50s	[40] [38] [30]✓ (26)	3 1
101	L72	D40 Pn	D60 Acc	L73	D70	D70 Ren	(50) [44]✓ (42) [38] (30) (?) N Ord	2 4
102	L65	D69 Ca	D30 Acc	D67 [CV]	D65 ○	D67 Pn	(45) [42]✓ (37)	1:2
103	L70	D30s	D30s TB	D79 ■	D50s Ca	D78 ■	○ [42]✓ (40)	1 2
104	L71	D60s (CV)	D60s [CV]	D48 Pn.	D50s Ren	D60s Pn.	[54]✓	1 0
105	D51 ●	D72	D76 □	L89	D74	D94	(59) [5]✓	1:1
106	L82	D85	D57 PA	L81	D40s Ca	D87	[52]✓ [C] D 42 N O d	2 0
107	D51 Acc	D65	D65	D74 [CV]	D65	D55 Acc	[51]✓	1 0
108	D70s ○	D	D	D70s □	D80s	D70s	□ □✓ [0]	3 0
109	L59 Db		D60s	D55 [CV]		D60s	□✓	1:0
110	L52	D33 TB	D58 [C]	D57 ■	D81 Ca	D83	[3]✓ (32)	1 1
111	L65	D73	D70s	L67	D70s	D60	[1] [36]✓	2:0
112	L70 Arth			D66 □			[Acc] b 2 [1] [38]✓ [37] [30] [28] (25)	6 1

(Unmatched Control Group—continued)

NO	MOTHER	MOTHER'S MOTHER	MOTHER'S FATHER	FATHER	MOTHER	FATHER †	PROPOSITUS & SIBLINGS	♂♀
113	L76 (CV)	D85	D77	D64 ⊥ Db	D81	D86 □	[55] [52] (46) [44]	3 1
114	L69	D71		D47 TB			(43) [42] (39)	1 2
115	L78 ●	D49 (hatched circle)	D93	D51 Acc	D55	D65 [CV]	[49] [41] [37]	3 0
116	L75 ○	D70s	D80s	D42 Acc	D80s	D70s	[48]↙ (45) [43] (40) [38]	3 2
117	L71	D80's	D70s	L73	D70's	D80s	(44) [42]↙ [40]	2 1
118	L70	D86	D56	D55 Pn	D87	D89	[51]↙ [Sep] D4 [Acc] DP N Od	3 0
119	L64 (hatched circle)			D65 [CV]			[38]↙ [7]	2 0
120	L60			D42 Pn		D73	[43]↙	1 0
121	D73 ● Db	D62	D78	D75 Ca	D65	D75	[42] (40) [39] [37] [35]↙	4 1
122	D42 Infect	D60	D55	D67 ■	D57 (CV)	D52 Pn	[34] [32]↙ (29) [23] [22] [20] (17) N Ord [◇◇◇] D1f	5 2
123	D52 Acc	D88 Ca	D90 Pn	D59 ■	D63 Ren	D74 ■	(44) [42] [41]↙	2 1
124	D63 Ca	D86 Pn	D83 Ca	D59 Park.	D61 Pn	D65 Pn	[49]↙	1 0
125	L56	D80	D67	D46 □			[32]↙ [27] [22]	3 0
126	L83	D74	D57	L83	D72 (CV)	D57	[48]↙ [◇ ◇] Stillb N Od	1 0
127	D66 (CV)		D30's	D82 Pn		D30s	(58) [51] (49) [46]↙ (hatched circle) D17 [Ren] D42 No Order	3 3
128	L65	D60s	D60s	L70	D60s	D60s	[36] [3] [33] [31]↙ [27] (24) ○ N Od D1f (21)	5 3
129	D36			D44 Db			[52]↙	1 0
130	D64 Liver		D57	D65 ■		D65 Pn	[44]↙ (43) (41) (40) [38] [30] N Ord [□ □ ○] S bor	5 4
131	L77	D50s Ren.	D60s	L78	D70s (CV)	D70s	[4]↙ (42)	1 1
132	D77 Ca	D90s	D50s	D80	D90s	)9(s	□ [Pn] D60 ○ [5]↙ [3]	4 1

133	L63	D65 ●	D76 Pn	L65	D86	D32 Acc	(35) [ ] [ ] [Ac] D20 [ ] D ○ (22)	4 3
134	L70	D67	D79	L69	D73	D51	(4) [ ] [35]	2 1
135	L66	D50s	D86	D60s [CV]	D60s	D60s	[46] [3] (43) [36] (26)	3 1 2
136	D56 Ca	D60	D92	D66			[42]	1 0
137	D60s Fist			D70s [CV]			[Acc] D14 (TB) D50 [48] (?) N Od	2 2
138	L76	D78	D76	L74			[2] [ ] D11 N Od	2 0
139	L68			L73			[40] [35] [33]	3 0
140	L74	D81	D66 Ren	D54 Ren	D65 Ren	D92	○ D11 [45] (44) [41] (40) (38) [36] (33)	4
							[Acc] D25	5
141	L73 Arth	D79	D85 Pn	D48 Ren	D68	D74 [C]	[48] [46] [45]	3 0
142	L64	L89	D79 Pn	L66	D55 ●	D85	[32]	1 0
143	L61 ○	D71 Ren	D80s Pn	D53 TB	D27 Ch B	D80s Pn	[33] (31) (26)	1 2
144	L74	D75	D61	L73	D77	D80	[44] [40] (35)	2 1
145	D55 (c)	D80 ●	D	D60 ■ Ob.	D80 ●	D82 Pn	[32] [31] [30] [28] (23)	4 1
146	D39 TB	D60s Ca	D	D44 TB	D40s	D40s	[32] (31) [Acc] D14 (29) [18]	3 2

(*Unmatched Control Group—concluded*)

APPENDIX D

Diet Record

QUANTITIES of all foods drugs tobacco and alcohol ingested were recorded by the interviewer on the accompanying form The amounts were then extrapolated to a weekly basis for the final recording and analyses For the coronary group records were made of food habits both prior to and after the coronary episode For the controls the usual diet was listed and any changes were noted

MASSACHUSETTS GENERAL HOSPITAL

Coronary Research Project No 6

series sex

name -

(Diet Card)

age - (no)

(1) Beef all forms
(2) Veal all forms
(3) Lamb all forms
(4) Mutton all
(5) Pork all forms
(6) Bacon strips
(7) Brains all
(8) Liver all
(9) Sweetbreads
(10) Frankfurts etc
(11) Specialty meat
(12) Salmon Swordfish
(13) Halibut Whitefish
(14) Lobster crab etc
(15) Scallops oysters
(16) Fats tallows
(17) Butter oleo
(18) Oils dressings
(19) Vinegar

(20) Eggs all forms
(21) Milk (per glass)
(22) Buttermilk
(23) Cream
(24) Cheese all
(25) Nuts all ex 26
(26) Peanuts
(27) Peanut butter
(28) Chicken
(29) Fowl ex 28
(30) Beans
(31) Coconut
(32) Candy
(33) Popcorn
(34) Coffee
(35) Tea
(36) Cocoa
(37) Beer
(38) Wine

(39) Liquor
(40) Cigarettes
(41) Pipes
(42) Cigars
(43) Digitalis
(44) Thyroid
(45) Sedatives
(46) Vitamins
(47) other
(48) Preferences

(49) Aversions

(50) Allergies

(51) Sugar protein carbohydrate or fat?

directions indicate measure (G-glass S-serving P-pat, O-oz.) and unit of time (Wk Mo Yr) preferably on weekly basis viz., Milk 14G-w O-rare or never

APPENDIX E

Summary of Case Histories

Case no	N ion- al ty	A at onset ( )	Dat & m	P ced com la	A vity onset	O upation before & f er	Compla at onse	D ree f pain	Radiation
001	Italian	35	1/23/ 2 8 00 m.	angina on effort	ld p tien on bed	male rse	substernal pain	severe	left elbow & fingers
002	I sh	40 6/12	5 30 1 3 00 p m.	none	pl ing baseball after ea g	lawyer	subs ernal pain, vomiting	severe	clavicles
003	Irish	39	12/26 40 8 00 p m.	none	walkin	male urse	substernal p in	moderate	upper abdomen
004	En l h	35 5 12	12 7 8 00 p m	ind gestio for 4 yrs. be m ush or hurry	alking	salesman	subs ernal pai	severe	forearms, elbows
005	English	35	3 1 9 12 00 noon	ang effort & af er d inkin hot drinks or eating heavy meals	alking	truck d ver	subs ern l pai	mode te	elbows, teeth, mandible
006	B tish Isles	33 12	10 1 1 00 m.	heartburn ind gestio fte tement heavy meals	lking p one fl h t reps	contractor & business agent no theatre manager	substernal pain, nausea, collapse, sweating	severe	both arms
007	Italian Irish	37	2 1 7 2 00 m	dyspnea on treme sertion onl	asleep	tool grinde	substernal pain	severe	left arm
008	Jewish	29	1 43 10 00 p m.	severe hest ain on strenuous xercise, adia in to both arms and h nds	dancing	soldier no man- ge & salesman, men clothing store	ternal pain	severe	arms
009	French British Isles	35	11 7 7 30 m.	hest p alking fas walkin after he vy meal, ind ges ion	walkin	ja itor no sa occu ion	substernal pain	severe	elbows, forearms, back
010	Jewish	40	12 30 5 9 00 p m.	none	at home	truck d iver	substernal pain	severe	none
011	I alian	36 8 12	2 70 45 11 30 m.	none	preparin troops for movement	army officer now accountant	dizziness uncon- scious m substernal pain	severe	upper abdomen
01	Old American	34	9 1/ t 2 30 p.m.	dyspne on xertion for 1 yr	pullin fire hose to scene of fire	gas station tend- nt	substernal pain	severe	both arms
013	I sh	3	9 23 38 00 m.	none	sleepin	truck driver now maintenance ma	indigestion, sub- sternal pain	severe	both arms

At the me when th report was undertaken, December 1 94 For complain as of December 1 1 3 see Append F
†Indic tes septal or lateral all involvement.
‡Normal roentgenogram.

Duration	Fluoroscopic & x-ray findings	C T ratio	Location of infarct	Rhythm	Conduction defect	Other ECG findings	Hosp home care	Change of diet	Recurrence	Present complaints & disability
3 mo., slowly by hypo	not remarkable, 3 1/47 3 19/42, 4 31/ 7	12 31	post.†	N.S.R.	none	none	MGH ks. home 5 ks.	yes	no	angina & dyspnea on effort
2 hrs.	10 49 slight incr transv diam. of heart; enlarged left vent.	15 3 31 2	post.†	N.S.R.	none	none	hosp 9 ks., inacti 6 mos.	yes f in, spices, fried foods	no	limited exercise
5 hrs.	2/26 48 N.R.†	15 31.5	pos	N.S.R.	none	none	hosp weeks	yes low chol-esterol	yes 1941 94	no strenuous acti ity
hr	3 1 49 pulsations dim. along left heart contour	16 33	post.	N.S.R.	none	none	home 6 ks., inactive mos.	yes star hes sweet	yes -/ 1 48	limited xercise
30 min.	3 .4 49 calcified scars in lung parenchyma bilater ally	1 7 30	post.	N.S.R.	none	none	none	yes low fat	no	occas. shortness of breath
2 hrs.	2/25/ 9 pulsations dim. alon border left vent. enlarged left vent. since last exam.	14 6 32.5	post.	N.S.R.	R B B	L.V.H	hosp. mo inactive yr	yes low f	no	angina on fort and citement, heavy meals
1 hr	3/17 9 not remarkable	1 3_5	ant.	N.S.R	none	none	home mo inactive mos.	yes low at	no	yspnea & palpitation on exertion
2 hrs.	49 sligh prominence of left vent.	15 30.5	ant.†	N R	none	L.A.D L.V.H. and strain	hosp. mo inactive 3 mos.	no	no	angina on mod. effort
1/2 hr	3 30/ 9 heart rate very rapid pulsations of small amplitude	15 30	post.	sinus tach ard ( )	none	none	inactive mos.	yes no eggs	no	angina on ef fort or excitement, no har work
2 hrs.	3/ 49 N.R	3 5 3	post.	N.S	none	L.A.D.	hosp wks., inactive mos.	yes	no	none
hrs.	2 1 48 linear streak in left mid-lung representing old scar	1 30 5	post.	N.S.R.	none	none	army hosp ks., inactive mos.	yes low cholesterol	no	angina pal-pitation on effort
2 hrs.	3 49 left ven wod, enlarged, aorta tortuous shows calcification in trans portion (2/ N.R.)	1 5	post.	N.S.R.	none	none	home wks., inactive mos.	yes. low fat	yes 94	elim. stren. acts
5 hrs.	5 calcifications seen in apical region of heart suggesting old pericarditis, enlarged left vent.	30	ant.	N R.	none	none	MGH wks., inactive yrs.	no	no	none

Cas	Nation-al y	A at ns (rs)	Dat & time	P ec d g om laint	A ty at onse	O upation before & /	Complai nat	Degree f pai	Radiation
014	Jew h	40	11/43 7 00 m.	none	s un waitin for bre kfast	sold no e- tired	subs rnal pai	moderate	none
013	B h Isles	37	12/?4/ 1 2 30 p m.	he vy feeli g in hea h le reasing f 1 yr	walking	salesman (h gh pressure) now off worker	substernal pa ll pe	severe	lower arm
016	I ah	32	5/5/27 11 00 m.	none	drivin ar	salesman	subs rnal pain	severe	none
017	Old American I ah	38	11/6/ 8 00 p.m.	te me dys ne limbin 3 flights & d ys befor	alking	machinist	faintness, fl tu-lence, awe ting, substernal pain	modera	none
018	British I les	40	2/28/44 9 00 m.	dyspn on reme xertion al-	run g f sun	in es men counsel	hea ness at chest	mild	none
019	B ish I les	37 8/12	9/9/46 10 00 m.	dyspne & p on ffort (lkin)	and re d in pape	mekeeper now unempl yed	sub ernal pain	seve	arms
0 0	J h	35	12/2 1 11 00 p m.	mode l sev in best 3 d ys bef re while han ing truck tir in cold and sno	sleepi	truck d ver	substernal pain, dyspne	sever	none
0 1	Old Ame ican	38	5/ 9 10 00 m	on ref ble to h C V A. in 1946	st nd g in urt oom	none pensioned b V.A	dizziness, sub-ste al ain	seve	left arm & hand righ arm to el-bow
022	J h	35	8 1 43 3 00 p.m.	preco dial gh ness & pain 3 d ys bef re wh le movin fa	alki g	fi nc ec ve	subster al pa we kness, swe	moderate	both arms & fingers
0 3	J ish	34	5/28 3 3 00 p m	angina ffort 1 yr befor onse ac tack	g in the tre	med l orderly U.S. Army no ho keeper	usea, substernal p n, vomitin	severe	left arm
0 4	Irish German	29 6 12	1/19 9 4 00 m	none	l g do	tor ( )) now en-gineer g den	usea, vomi un bsternal pain	moder	both arms, back, left ar
0*5	J h	25 6/12	5/21/47 1 00 p m.	ind ges ion for 1 ye hea ains oc asion-f ter uous work	alk p at ru	rmy office no tuden	substernal pain	mode te	arms
0*6	Syr	37	3/15 9 6 00 m	dyspnea on ertion	eating (ork	mach ne ope tor has no resumed work	substernal pain	moderate	in back between shoulders
0 7	B itish Isles German	3	4 43 11 00 p m.	as in ess on xertion	lying down	pl mbr contractor	substernal pain	severe	both arms to fingers
0 8	Jew h	30 8/12	8 12/46 8 30 m.	none	aris g fr m bed	store m ger	substernal pain	severe	left arm, fingers
0*9	Old Amer an	39 9 12	1/17/44 11 30 p m.	none	sleepin	hysician	nause vomitin substernal pain	severe	none
030	Old American	54	4/24 5 3 00 p.m.	none	limbin to bridge of submarine (2 fl gh)	na al officer now student lawyer	substernal pain nausea	moderate	forearm, fingers, throat

Duration	Fluorosco ic & x-ray find gs	C T ra io	Locatio f infar	Rhythm	C ductio d f is	O h ECG findi	H p ho car	Change f diet	Recurrence	Present complaints & disability
1 hr	2, 49 pulsations dim. alon left border enlarged left vent.	1 33	post.	N S R.	partial A V block PR int. 0 *2	none	arm hos 3 1 2 mos., till in ac	yes no f	no	occas. pain in chest & lower arm
2 hrs.	1 10 48 N R.	15 33.5	pos †	N S R.	none	L V H & tru	hosp 6 ks. inac ve 6 ks.	no	yes /3 – inactive 1943	elim. stren. activity
2 hrs	5 14 enlarged left ven	16 30	an	N.S R.	none	none	hosp ys, home 6 ks inac ve 2 mos.	no	yes 1929	partly crippled by gout
1/2 hr	1 26 49 lef ven enlarged, aorta tortuous, lung fields suggest bronchiectasis	14 29	pos †	N S R	none	none	home 2 ks.	yes low calorie	yes	died of myocardial infarction
1 mn.	not markable, 1 44 9 5 1 8 46, 8 30 8 /17 49	12.2 ,2	an	N S R.	none	none	MGH 1 d ys, ina ve ks.	yes elim ho es ter ls	no	lim. ac ve sports
2 hrs.	5 11 49 N R.	3 27 5	post.† ant.	inus tac y-cardi	R B B	occas. P V C.	os mos., inactiv 1	no	yes 9 25/46	yspnea & an na on effort
2 hrs.	2, 8/49 N R.	13 8	post.	N S.R.	none	tenden to R A D	home mo ac ve 7 mos	no	no	engina on effort
1 wk.	5 11/49 N R.	15 34	pos †	N.S R	none	none	hosp 2 mos.	no	no	best pain, yspne on exertion
4 hrs.	9 40/ 5 N.R.	—		N S R.	none	ne	me ks. inac ve ks.	yes low holesterol	no	m. stren. activity
hrs.	—	—	an	N S R.	none	L A D	hos 3 mos. inac 3 mos.	yes low f	no	occas. heat pain on effort
1 hrs.	5/26 49 N R.	5	pos	us brad ard	ne	none	osp 5 ks. la hosp mos.	no	no	none, elim. stren. serane
1 hr	5/17 N R.	15 5 3	post	N S R.	none	none	osp k.	yes lo calorie	yes 5 7	none
18 min.	5/3/ 9 left ven arkedly n-larged lun markings accentuated, pulmonary ves. engorged	18 5 33		N.S R	none	none	MGH 7 s. remains inac ve	yes elim. f	no	dyspnea, palpitation on exercise
1. hrs.	—	—	post.	N.S R.	none	none	hosp 7 ks., inac tive mos.	yes low salt, low cholesterol	yes 2. 5 1	dyspnea, no physical exertion
hrs.	5/2/49 sligh incr in AP diam. of chest	15 3 5	an	N.S.R.	none	none	no	yes low fa	no	none
hrs.	1 /7/48 left ven enlarged, pulsations absen along border left vent., representing thinned out myocard um	.2	ant.	N.S.R.	L B	L H.	hosp 6 wks., inactive 3 mos.	yes low cholesterol, salt free	yes 44 7	limited work, no exercise
6 hrs.	8/24 48 N R.	13 5 32.5	post.	N S.R.	none	none	hosp. 2 mos., inactive mos.	yes low fat & cholesterol	no	—

Cas no	Nation-al ty	A at on (yrs.)	Dat & m	P eding complain	A ty at ns	Occupation bef re & f er	C mpla at onset	D gree f pain	Radiation
031	B tish Isles	38	3/44 3 00 p	none	cking	labor foreman	substernal pain	moderate	none
032	J ish	40	8/9/47 12 30 a.m.	pains arms ff	slee ing	lec ricia	subs ernal pain	severe	arms, fingers
033	B itish Isles Irish	36	2/48 7 00 p.m.	angina pectoris on ff rt	lking in deep snow	mach nis	substernal pain	moderate	left arm & wris
034	J wish	55	12/46 00 p.m.	marked weigh gain, marked growth f facial hair f ll ing G B per tion	shovel g coal	housewif	bsternal pain	severe	none
035	Old Amer an	40	11/17/47 5 00 p.m.	3 acks f ind ges-tion 1 yr prior onset and dyspne ff	esting in bed	machine oper to now machine in-spector	subst rnal pain, choking	severe	arms & hands
036	F nch	36	3/45 2 30 p.m.	none	lking to work	boiler maker no woole ft ubee	substernal pain	moderate	none
037	J ish	37 4 12	2/25/45 1 30 p.m.	dizziness, f gue, dyspnea on walki g through snow on xertio	l ying ards	lec ee arrier	substernal pain	severe	none
038	Jewish	3	9/25 3 8 00 m	none	alking	salesman	substernal pain, indigestion, fl ulence	severe	none
039	Old American British Isles	38	5/1/ 7 8 00 p.m.	p in in chest, mb-ness in arms whe walk g in cold occasionall rest	lif ing he vy tables in orkshop	l wyer	bsternal pain	severe	none
040	B tish Isles Irish	33	10 1/44 3 00 p.m.	f ue, dyspne on ertion 1 yr	mac hin p h ll	soldier no hotel ma ge	substernal pain	severe	none
041	J ish	40 11/12	1/12/46 8 00 m.	ind gestion, cons pa-tion, f gue 1 yr angina 1 mo.	maki home calls	physician	substernal pain, syncope p lpi ion	moderate	none
042	J ish	38	11/25 37 7 00 m	none	in at desk, wo king	restaur teur	substernal pain, indigestion	moderate, then severe	—
043	Arme ian	37	9 1/42 10 00 p.m.	angina 2 ks.	mopping floor	head waiter in restauran	substernal pain	severe	left arm & hand
044	Jewish	57	3/17/44 2 30 a.m.	none	sleepi	salesman	substernal pain	severe	elbows
045	Portuguese	38	10 3 8 00 p.m.	none	makin home & office alls	physician	weakness & nausea	none	none
046	Irish	34 8 12	4/46 7 30 m.	none	gettin out of bed in mornin	lawyer	nausea, headache, numbness, left arm	none	numbness, left arm
047	Old American	54	12/17/46 2 00 p.m.	dyspne 2 mos. before & ache in arms, shoulders, stomach	working dr fting table	mechanical engineer	substernal pain, aches in arms & shoulders	moderate	arms & shoulders

Duration	Fluoroscopic & x-ray findings	C T ratio	Locatio f infar	R thm	Conductio defec	O her ECG findin	H home ar	Chan f diet	Recurrence	se om lain & d ability
12 hrs.	10 22 47 lef vent. enlarged	1 27	pos	N.S.R.	impaired intraven regular conduction 0 11 sec	L.V.H. & strain	h me k	yes sal f ee, low h les-terol	1/45	died 1949
hrs.	1 22/ 7 cal-cification both apices, left vent. enlarged	1 5 3	an	N.S.R.	none	none	hosp 6 k ina. 6 mos	yes low holes-ter l	no	occas. in ches
3 mos.	5 5/49 slight prom. of left vent., lun fields lear	14 31 5	pos	N.S.R.	none	none	me 2 ks inactive 5 ks.	yes low f & choles-terol	no	an on ff & exc temen
hrs.	10 "1/47 not remarkable	14 28 5	post.	N.S.R.	R BBB	none	none re-duced amt. of house-work	yes low calo ie	no	pain in ft arm, hest & pal tion tren. exertion
7 hrs.	1 49 N.R.	79 5	an	N.S.R.	partial A-V block	none	hosp 5 1 2 ks., inactive 7 mos.	no	no	spells f zziness and itation
3 mos.	10 28 sligh prominence in region of left vent.	14.5 30 5	post.	N.S.R.	none	L.V.H.	none, con work	yes low f	yes 946	an na pector dail 300 tabs. nitro-glycerine per
8 hrs.	1 29/ N.R.	1 30 2	ant.	N.S.R.	none	none	hosp mo inactiv 3 mos.	no	no	none
3 hrs.	1 /4 aorta tortuous, enlarged lef vent.	18 3	pos t an	sinus P.V.C.	Q S 1	L.A.D L.V.H. & strain	hosp ks., inactive 3 mos.	no	yes 9 2	died 1948
hrs.	1 /1 9 pulsa-tions dim. along border of lef vent., prominent aortic arch	1 3	an	N.S.R.	none	none	hosp 2 mos., inactive 3 mos.	no	no	none
2 hrs.	1 2, N.R.	13 5 35	an	N.S.R.	none	none	hosp 9 wks., inactive 3 mos.	yes low choles-terol	no	none
12 hrs.	11/1 7 N.R. 1/29/48 N.R.	3 9 29	an	N.S.R.	none	none	MGH 3 ks., inactive 3 mos.	yes low cholesterol	no	slam. strun. sports
—	5 "9 48 N.R.	12 4 27 5	ant.	N.S.R.	none	none	hosp 6 ks., inactive 1 yr	yes low choles-terol	no	none
2 1 2 hrs.	1 /20/ N.R.	1 5 30	ant.	N.S.R.	none	none	hosp. 3 wks., home	yes	yes 5	angina on effort
1/2 hr	7 enlarged left vent.	3.5 28	post.†	N.S.R.	none	none	hosp 5 ks home wks., inactive 2 yrs.	no	no	can walk fast, run, climb stairs
none	1 /25 slight prominence in re-gion of left vent.	1 3	post.	N.S.R.	none	occas. P.V.C.	home 6 wks., inactive 3 mos.	yes	yes 946	all activities limited
24 hrs.	1 /25 dural clips along both sides of lower dorsal spine	13 32	post.	N.S.R.	none	none	hosp wks.	no	no	can climb stairs
7 hrs.	12/1 7 not re-markable except C-T ratio enlarged left vent.	1 27	ant.	N.S.	- - - -	L.V.H.	hosp 2 wks., home ks.	yes	no	died 7 '48

Case no	Nation-al	Age (yrs)	Date & time	Previous symptoms	Activity at onset	Occupation before & ...	Complaints	Degree of pain	Radiation
048	Old American	46 10/12	6/47 1 00 a.m.	angina, dyspnea 3 yrs.	sleep g	house d	substernal pain	severe	none
049	Old American	40	1/14/47 7 00 p m	chest p ns 4 yrs. on ert p eviously treated for Buerger' disease	& moking	truck ines ac od	pallor substernal pain, nausea, vomiting	severe	left arm, upper abdomen
050	Old American	32	4/17/46 11 00 m.	none	nding business meeting	il sec tire	substernal p n	moderate became worse	left arm & shoulder
051	I alia	36 6 12	5 3 7 1 00 p m.	indigestion several k before, nervous tension, f gue	eating	truck driver	nausea, vomiting, cyanosis, substernal pain	moderate	forearms felt dead
052	Old American	33 8 12	1/20 5 8 00 p m	thyr idectom 1938	workin in office	lawyer	nausea, syncope substernal pain	mild	none
053	I sh	33	10/9/46 9 30 m.	none	gett g ou f bed in mornin	medical tude ow hysician	substernal pain	modera	throat, wrists, teeth, ja
05	Jewish	26 10/1	12/21/47 9 00 m.	f gue 6 mos pre- in ches on ert	ash g cars, smoking	gar ge pe tor no salesman	h ry pressur in hest	mild	none
055	Irish	33	10/24 5 10 00 m	gina xertion f months before	lking around mach ne shop	tannery m hin for ma	dizziness, substernal pain	moderate	none
056	B ish Isles	40	1 19 5 2 30 m	g ffort 3 yrs. befor	alking hil	hemist now teacher f hem try	pain in jaws, chest p essure	moderate	ri ght shoulder
057	French Irish	35	8/1/39 8 00 m	none	bu lin	cook	substernal pain	severe	left shoulder
0 8	Irish	38	7 21 40 12 noon	ns in lef arm for 1 yr	wo king in ffice	ffice ma ger	substernal pain	moderate	left arm
0	Danish	41	11 10 44 1 00 p m	dyspnea and ind gestion wh le ork 1 yr bef re	and talk in on box	fisherman	nausea, substernal pain	severe	upper arms, throat
060	J sh	34	11/17/ 5 1 00 p.m.	none	layin touch football	manage indu- tr al firm	bsternal & upper abdominal pain	severe	none
061	Jewish	40	10/12/40 2 00 m	none	alking up h ll	owner thermometer factory	d ll pressure in hest	moder to severe	none
06	I alian	29	1 11/ 8 12 noon	dyspne and angin on effort	restin during lunch hour	brazier now unemployed	substernal pain	severe	left forearm, fingers, bac
063	Irish	59	1/20/ 8 3 00 a.m.	f gue for few mos	whi le ork and dri kin coffee	machine oper tor	substernal pain, nausea, fatigue	sever	through to back, arms fe dull
064	Jewish	39	12 11 46 8 30 m.	heartburn for 2 yrs.	orking in factory	laborer	heartburn, profuse perspiration	moderate	none
065	Danish German	27 5/12	9 18 5 10 30 a.m.	occasional pain in left arm associated ith strain xercise	walked 1/2 mile carrying heavy suitcase	military pilot now airport manager and fligh instructor	substernal pain	severe	none

Duration	Fluoroscopy & x-ray findings	C T ratio	Location of infarct	Rhythm	Conduction defect	Other ECG findings	Hosp or home care	Change of diet	Recurrence	Present complaint & disability
	1/6 48 N.R.	—	an	N.S.R.	none	R.A.D.	home	yes low choles-terol	yes 1/48	died 1/48 MGH under stud & obs.
hrs.	1/1 8 N.R.	12.8 31	post.	N.S.R.	none	none	hosp 4 wks., inactive 8 mos.	yes low sal & holes-terol	yes attacks than mos.	died 3 7/ 9
mild 12 hrs, severe 3 hrs.	1/27 48 N.R.	12.5 30	ant.	N.S.R.	none	L.A.D.	hosp 1 mo inactive 3 mos.	no	no	none con-tinues stren. sports
hrs. of ...	1 30 48 area of increased den- 2nd lef interspace	13 8 32	an	N.S.R.	none	none	home 6 ks.	yes low h les-rol	no	occas. mild substernal pain
hrs.	2 3 48 2 6/49 modera ly en-larged left ven	15 5 31	(ld) pos (new)	N.S.R.	none	none	home 1	no	yes 9/ 7	elim. stren. sports
hrs.	5 11 48 N.R.	13 32	post.	N.S.R.	none	none	home ks. inac ve 0 ks.	yes lo holes-terol	no	elim. stren. sports
1 hrs.	2/13/48 sl gh prominence of left vent. co ponent	15 2 28 6	an ?	N.S.R.	none	L.A.D.	home k., hos 0 days, inactive mo	no	no	tires easily on exertion
hrs.	2, 3/48 sligh accentuatio of vascular markings	14 30	an	N.S.R.	none	L.A.D. L.V.H.	hosp 4 ks. home 2 1/2 ks.	no	no	ni oglycerine daily for angina
1 hr	2 1 8 N.R.	12 5 31	pos	ni tac y ardi	none	none	none	no	no	fatigue, probabl psy-chological
½ mn.	18 48 sligh prominence f left vent. component	4 32	post.	N.S.R.	none	none	osp ks. ac ve 1 yr	yes no f ts, low choles-terol	no	lim. stren. sports
few hrs.	1 1 /48 lef vent. enlarged, vascular markings prominen	6 5 31	an ?	N.S.R.	none	none	hosp mo home mo inactive 3 mos.	no	no	elim. stren. sports
½ mn.	2/26 48 5 aorta dilated & tortuous en arged le ven	16 5 3 5	pos nt.	N.S.R.	none	none	home s. inactive mos.	yes low fat	yes 1 7	dizziness, dyspnea
2 hrs.	3 5 sl ghtl enlarged left ven	1 2 30.5	pos	N.S.R.	none	none	hosp 6 ks. inactive yr	yes low fat	no	[illegible], elim. sports
10 mn.	3 6 gh tortuous f aorta	13 30.5	post.	N R.	none	none	home mo.	no	no	elim. rest. sports
1 2 hrs.	3 N.R.	5	post.	N.S.R.	none	none	hosp mos., inactive 1 yr	yes low choles-terol	—	severe angina on effort, dyspnea
6 hrs.	none obtained	—	post	N.S.R.	none	L.A.D. 30	home 1 mo.	no	yes	died 3 ½ 49 of myocardial infarction
4 hrs.	3 1 48 prom-inence in left vent.	9	post.	N.S.R.	none	none	hosp 5 wks., home 7 wks.	yes low salt	yes 10 13	died 3 1 49
24 hrs.	3 48 apparent prominence in left vent.	3 30 0	post.?	N.S.R.	none	none	hosp 6 wks., inactive 3 mos.	yes low choles-terol	no	none

Case no.	Nationality	Age at onset (yrs.)	Date & time	Preceding complaints	Activity at onset	Occupation before & after	Complaint at onset	Degree of pain	Radiation
066	Germa	36	4/18 7 7 00 p.m.	chest pains & aching in both arms while working	working on automobile	auto mechanic	substernal pain	severe	both arms
067	German English	39 1/12	3/1 46 6 30 a.m.	none	in bed	farmer	substernal pain	severe	arms, back of neck
068	French British Isles	39 11 12	5/7 7 1 00 .m.	dyspnea on climbing steps or walking rapidly	sittin at office desk	electrical engineer	substernal pain	moderate	forearms
069	English French	35	12/9 43 5 00 p.m.	pain in arms on exertion 6 mos. before	walking	diesel engineer	substernal pain with radiation to arms	moderate	arms
070	Jewish	36 10 12	11 15/ 2 5 00 p.m.	pain radiating down left arm after day' work	walking	real estate operator now salesman	extreme dizziness, no pain for 30 min.	severe after 30 min.	left arm from elbow to wrist
071	Italian	31	7/9/46 -00 p.m.	angina on exertion with radiation to arms 2 yrs.	pl ying ball	soldier now laborer	substernal pain	moderate	arms
07*	German	34	7 15/ 7 2 00 p.m.	none	working in garden	airplane parts and maintenance	substernal pain, heartburn, dyspnea	moderate, severe	arms
073	Old American	37	12/27 46 3 00 a.m.	indigestion for 1 yr chest pain on xertion associated with dyspnea	sleeping	sales representative	substernal pain	severe	left ulnar nerve distribution
074	Ital	40	1 14/44 3 00 p.m.	none	ting on toilet, read ng	used car dealer	substernal pain	severe	none
075	British Isles	31 6/12	8 6/40 9 30 a.m.	none	lifting heavy objects	electrician	indigestion, substernal pain	modera	upper abdomen
076	Jewish	34	4 7 48 30 a.m.	angina on effort, 944	lying in bed	machinist	heartburn, substernal pain	moderate	arms, hands
077	B itish Isles	3	5/2 / 7 00 p.m.	severe pain in lef arm while dri ing car 2 mos. before	ting in barber shop	service station operator	substernal pain	severe	left arm and fingers
078	Jewish	3	11 15/ 8 9 30 p.m.	dyspnea on climbing 1 fl gh of steps	ting, talking	salesman, desk work	substernal pain	severe	none
079	British Isles Danish	33	6/27/3 3 00 p.m.	dyspnea while playing tennis	lay ng [illegible]	contractor	substernal pain, dyspnea	very severe	none
080	Jew h	38	3 13/ 7 3 00 p.m.	sligh dyspnea prior to acute attack	driving automobile	physician, now hours work	substernal pain	severe	none
081	Irish	35	1 '28 46 00 p.m.	none	ridin on elevated	painter now watch maker	heartburn, substernal pain	severe	to right hand and thumb
082	Austrian	36 5/12	1.. 4 6 00 a.m.	angina 2 yrs. on strenuous work or excitement	sleeping	machinist	heartburn, substernal pain, sweating	moderate	none
083	Irish	34	7/23 44 11 00 p.m.	none	digging foxhole	soldier now clerk and salesman	substernal pain, dyspnea	severe	none

Duration	Fluoroscopic & x-ray findings	C T ratio	Location of infarct	Rhythm	Conduction defect	Other ECG finding	Hosp. or home care	Change of diet	Recurrence	Present complaints & disability
3 hrs.	3/18 48 N.R.	12 8 29	ant.	N.S.R.	none	none	hosp wk., home 1 mo inactive 2 mos.	no	no	none
1 hrs.	3/23/49 N.R.	13 5 30.5	an	N.S R.	none	L.A.D	home 6 ks., inactive 1 yr	yes low f	no	none
1 hrs.	3/24/48 N R.	4 33	post.	N S R.	none	none	hosp 5 ks., inactive 5 wks.	yes	no	none
survived days	3 24 48 N.R.	12 29.2	post.	N.S.R.	none	none	none	yes low choles-terol	yes	died /10/48
1 hrs.	3/3 / 8 N.R.	1 31 5	post.	N.S R.	none	none	home 6 ks., inac ve mos.	yes less quantity	no	elim. stren. sports only
hrs.	/13/48 slightly enlarged left vent.	1 .2 6	post.	N.S R.	none	none	none	yes low choles-terol	yes	died 1948
min	/1 /48 N.R.	.5 79	an †	N.S.R.	none	none	none	yes low choles-terol	no	none
	/1 8 N R.	31	post. & ant.	N S.R.	none	none	hosp 5 wks., inactive 6 mos.	yes low caloric	yes 1 8 00 .m.	occas. heat pain, elim. all exercise
hrs.	/22/48 N R.	3 30	post.	sinus brad cardia	none	none	hosp 2 mos., inactive yr	yes low choles-terol	yes 9 44	occas. heat pain on xertion, lim. sports
min.	/22/48 slightly enlarged lef ven	3 25	ant.	N.S.R.	none	none	home 1 mo inactive mos	no	no	elim. sports, no other complaints
min.	8 48 N.R.	—	ant.	N.S R.	none	none	none	no	no	none
5 hrs.	28 48 slight incr in trans. diam., enlarged left ven	26	ant.†	N.S R.	none	L.A D	hosp 2 mos., inactive mos.	yes low holes-terol	no	chest pain on exertion or after over eating
0 hrs. until oxygen was ven	5 6 48 enlarged left vent., gh tortuosity of aorta	32	ant.†	N.S R.	none	none	hosp 6 1/2 wks. inactive 6 mos.	yes low fat	no	palpitation, dyspnea on xertion
hrs.	5 paradoxical pulsation along border of left vent. cm. above apex	12.5 30 5	ant.†	N.S.R.	none	none	home in bed, inactive 3 mos.	no	yes	elim. ac ve sports
72 hr	5 48 transv heart within sthenic thorax	6 5 .5	post.	N.S R.	none	none	hosp 3 wks., inactive mos.	yes low choles-terol	no	occas. pain & pain after exercise
12 hrs.	/ 1/48 N R.	—	post.	N S R.	none	none	hosp 1 mo.	no	no	mild angina
3 hrs.	6/24 48 pleural thickening left costophrenic angle; regeneration 5th left rib for old empyema	1 .2 31.5	post.	N S R.	none	none	hosp 2 1/2 ks., home 3 wks.	no	no	occas. chest pain on ef ort
24 hrs.	5 3 48 transv heart, slight prominence of left vent.	5 31	post.	N S R.	none	L.A D	hosp mos., inactive mos.	yes low choles-terol	yes	

APPENDIX F

Follow Up Study of Coronary and Unmatched Control Groups

Coronary Group

A STUDY was made of the status on December 31, 1953 of the *original 100 patients with coronary heart disease* * The results were as follows

Status of 100 patients on December 31 1953 (97 male 3 female)

	Dead	*Alive*	*Whereabouts unknown*
Men	21	62	14
Women	2	1	0

All the deaths of both men and women resulted *from coronary* heart disease

Duration of survival following initial coronary episode in the 21 men known to have died

Duration of survival in months	*No of men*
0– 12	0
13– 36	5
37– 72	5
73–108	5
109–147	6

It will be observed that for the 21 men who expired the average survival period following the initial coronary episode was 6 years and 6 months with a range from 16 months to 12 years and 3 months The 2 women who expired survived 7 months and 49 months respectively

*The authors are indebted to General Lewis B Hershey Director National Selective Service System for his cooperation in tracing members of both coronary and control groups

Survival period following initial coronary episode in the 62 men known to have survived

Duration of survival in months	*No of men*
42–60	4
61–72	11
73–84	10
85–96	10
97–108	7
109–120	3
121–132	5
133–144	4
145–156	2
157–168	2
169–180	1
181–192	1
193–204	1
320	1

The average survival period to December 31 1953 was 8 years and 7 months with a range from 4 years and 7 months to 26 years and 8 months (The median survival was 8 years and 7 months)

Main symptoms among the 62 men known to have survived

	No of men
Main symptoms	
dyspnea on exertion	13
residual angina pectoris	22
indigestion only	1
Activity	
full day s work	57
partially disabled	5

The 1 remaining woman carried on her household duties

Unmatched Control Group

Responses from 130 of the 146 men who comprised the un matched control group revealed that as of December 31 1953 all were working Seven had symptoms which may be interpreted as angina pectoris while 4 others had left precordial pain of non specific character One had experienced a myocardial infarction

As a group the unmatched controls had not undergone any severe illnesses Three had had major elective surgery with complete recovery two minor surgery with no dire consequences

Index of Subjects

Letters following page numbers indicate
a—*appendix* fig—*figure* t—*table*

Index of Names